Official Title:	**ISIS 304801-CS7 The APPROACH Open Label Study Volanesorsen (ISIS 304801) An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients With Familial Chylomicronemia Syndrome (FCS)**
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ISIS 304801-CS7

The APPROACH Open-Label Study

Volanesorsen (ISIS 304801)

An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol Amendment 10 - France – 01 May 2019

EudraCT No: 2015-003755-21

ISIS 304801-CS7

The APPROACH Open-Label Study

Volanesorsen (ISIS 304801)

An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol Amendment 10 - France – 01 May 2019

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Protocol Amendment 9: 25 May 2018

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Akcea Therapeutics, Inc.

Protocol Number: ISIS 304801-CS7

Protocol Amendment 10 - France

EudraCT No: 2015-003755-21

Clinical Phase: 3

The APPROACH Open-Label Study

Volanesorsen (ISIS 304801)

An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

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Date: 01 May 2019

Confidentiality Statement

This document contains confidential information of Akcea Therapeutics, Inc. and Ionis Pharmaceuticals, Inc. that must not be disclosed to anyone other than the recipient study staff and members of the independent ethics committee, institutional review board, or authorized regulatory agencies. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Akcea Therapeutics, Inc. and Ionis Pharmaceuticals, Inc.

Protocol Signature Page

Protocol Number:	ISIS 304801-CS7
Protocol Title:	An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Amendment:	Amendment 10 - France
Date:	01 May 2019

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)", Amendment 10 – France, dated 01 May 2019, and agree to conduct the study as described herein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice E6 (R2).

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Akcea Therapeutics, Inc. and Ionis Pharmaceuticals, Inc.

Investigator's Signature

Investigator's Name *(please print)*

Date (DD Month YYYY)

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PROTOCOL AMENDMENT

Protocol Number:	ISIS 304801-CS7
Protocol Title:	An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Amendment Number:	10 - France
Amendment Date:	01 May 2019

The purpose of this protocol amendment is to implement the following modifications to Protocol ISIS 304801-CS7 Amendment 9 - France dated 25 May 2018:

- To add an up to 52 weeks of additional treatment to the Extended Treatment Period, to clarify the option for patients to receive a volanesorsen dose reduction of 300 mg every two weeks, to clarify discontinuation of patients from the treatment period who are on a dose pause for ≥ 3 months, and to remove the references to landmark visits (if patient stops treatment then they enter the follow-up period).

Minor changes (not included in the list of changes below) have been made throughout the protocol to correct errors and/or to improve the overall clarity of the original protocol but these changes do not impact subject safety, exposure, or the overall study design.

The following table provides a summary list of major changes to the protocol, additions are indicated as underline and deletions are indicated as strikethrough:

Protocol Section	Description of Change	Rationale
Section 2.3.4 Clinical Experience	~~Volanesorsen has been evaluated in one Phase 1 study and two Phase 2 studies, all double blinded and placebo controlled. The total exposures comprise 99 patients and healthy volunteers administered volanesorsen from 50 to 400 mg subcutaneously up to 3 months (compared to 37 administered placebo).~~The clinical experience with volanesorsen includes clinical trials in healthy subjects, patients with hypertriglyceridemia, FCS, or familial partial lipodystrophy. Overall, 431 patients and healthy volunteers have taken part in the clinical development program, of whom 325 have received at least 1 dose of volanesorsen. Ninety-five (95) patients with FCS have been enrolled in studies, all showing clinically meaningful reductions in plasma triglyceride. Patients with FCS continue on treatment in the open-label extension (OLE) and triglyceride reductions persist at similar levels as reported in earlier studies. In the completed Phase 1 and Phase 2 studies, volanesorsen was well-tolerated and demonstrated a favorable safety profile. There was no clinical or laboratory evidence of drug-drug interactions despite many patients in the Phase 2 clinical trials receiving	Update language regarding clinical experience in Phase 1 and 2 studies and incidence of AEs in completed Phase 3 studies and update to language regarding safety risks of Study Drug.

	concomitant medications that are known to be associated with elevations in hepatic enzymes, such as fibrates and statins. There were no volanesorsen-associated laboratory abnormalities suggestive of an effect on the renal (serum creatinine, proteinuria) or hepatic systems (alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin). There was a reduction (mean reduction < 30%) in platelets in volanesorsen vs. placebo with mean nadirs for all doses remaining above the lower limit of normal (LLN). The most frequently reported adverse events (AEs) were mild, non-progressive events at the injection site. In Phase 2, a single serious adverse event (SAE) of secondary serum sickness-like reaction was reported as related to Study Drug. … In the completed pooled Phase 3 studies (ISIS 304801-CS6 (hereafter referred to as CS6) and ISIS 304801-CS16 (hereafter referred to as CS16), the most common AEs associated with volanesorsen administration were tolerability at the injection site and platelet reductions. The majority of the injection site AEs were mild, none were severe, and the incidence appeared to decrease over time. No deaths have been associated with volanesorsen treatment to date. No cardiac toxicity was associated with volanesorsen treatment. There were no abnormal QTc findings and no study-drug related adjudicated major adverse cardiac events (MACE). There is no evident association between volanesorsen treatment and changes in renal or liver functions.~~In clinical studies conducted to date volanesorsen has been well-tolerated and has shown a favorable safety profile. There has been no clinical or laboratory evidence of drug-drug interactions.~~ The safety profile of volanesorsen has been well-described in this development program, which has identified 3 safety risks: thrombocytopenia (an identified risk), constitutional symptoms (flu-like reactions and influenza-like illness), and injection site reactions (a tolerability signal). Spontaneous, mild to severe thrombocytopenia has been described in the FCS patient population (Gaudet et al. 2017) but is increased by treatment with volanesorsen. Less frequent and less pronounced platelet declines were also observed with volanesorsen treatment in the hypertriglyceridemic (HTG) population of CS16. When fully complied with, frequent monitoring for this effect and appropriate dose adjustments have been successful both in preventing and promptly detecting the occurrence of severe platelet declines and often in retaining patients on treatment.~~In the completed studies there have been no volanesorsen associated laboratory abnormalities suggestive of an effect on the renal (serum creatinine, proteinuria) or hepatic systems (alanine	

	~~aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin). In Phase 2 studies, there was a mild decrease of platelet count associated with volanesorsen administration that recovered in the post-treatment period and was not associated with platelet-related adverse events (AEs). In the blinded ongoing clinical trials of ISIS 304801, 2 patients of 142 dosed (as of February 29, 2016) had a decrease in platelet count to less than 50,000/mm3 in the absence of major bleeding or clinically relevant non-major bleeding and had Study Drug paused as per the monitoring and stopping rules for platelet counts (Section 8.6.3). Platelet counts recovered following suspension of dosing.~~ ~~The most frequently observed AEs with volanesorsen were local reactions at the injection site. Local cutaneous reactions at the injection site defined as those events presenting as either pain, tenderness, erythema, pruritus or swelling occurring on the day of injection and persisting for at least 2 days were infrequent (~15% of injections), were almost always mild, resolved spontaneously, were non-progressive, and were not associated with systemic sequelae.~~	
Section 2.4 Rationale for Dose and Schedule of Administration	The dose and schedule selected for this study is 300 mg per week for 52 weeks, with the option of continuing ~~dosing~~treatment for up to an additional ~~52~~104 weeks. The dose of 300 mg per week and dose reduction of 300 mg every 2 weeks (delivered as a single 300 mg dose) are ~~is~~ supported by both the cumulative nonclinical data available to date and the Phase 2 clinical data. ... ~~No non~~Non clinical findings were not considered to be related to the pharmacologic inhibition of apoC-III. ... In addition to the nonclinical and clinical experience of volanesorsen, the dose and schedule of administration is supported by the preclinical and clinical safety experience of several other 2′ MOE-modified ASOs that have been ~~safely~~ administered intravenously and subcutaneously in multiple clinical studies at doses up to ~~1000~~1200 mg and for treatment durations that exceed 24 months (Santos et al. 2015).	Language added to clarify dose reductions as 300 mg every 2 weeks according to patient's tolerability on the 300 mg weekly dose, given similar extents of triglyceride lowering anticipated based on population pharmacokinetic/ pharmacodynamic model-based simulations. Updated to reflect data presented in source listed.
Synopsis: Study Design, Study Visit Schedule and Procedures	Synopsis All patients will receive volanesorsen 300 mg once per week for 52 weeks. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period. Following the Week 52 visit, patients will have the option to continue ~~dosing~~ treatment for up to an additional ~~52~~104 weeks for a total of up to 156 weeks of ~~dosing~~ treatment. Patients not continuing	Edited length of Extended Treatment Period to allow patients in France to continue to receive study drug until commercialization of product.

Section 3.1 Study Design Section 6.1.3 Extended Treatment Period	~~dosing~~ treatment will enter a 26-week post-treatment follow-up period. Section 3.1 Following the Week 52 visit, patients will have the option to continue ~~dosing~~treatment for up to an additional ~~52~~104 weeks for a total of ~~104~~up to 156 weeks of ~~dosing~~ treatment. Patients not ~~to~~ continuing ~~dosing~~ treatment will enter a 26-week post-treatment follow-up period. Section6.1.3 After completion of the Week 52 visit assessments, patients will have the option of continuing ~~dosing for up to an additional 52 weeks~~ treatment for up to an additional 104 weeks. For patients that have entered the Extended Treatment Periods, study participation will be up to an additional 104 weeks or until commercialization of product, whichever is sooner. During the extended treatment period, patients will have assessments and procedures done during Weeks 54-~~104~~156 as per the Schedule of Procedures in Appendix A	
Section 3.4.3 Extended Treatment Period	Following the Week 52 visit, patients will have the option to continue ~~dosing~~ treatment for up to an additional ~~52~~104 weeks. Patients not to continuing ~~dosing~~ treatment will enter a 26-week post-treatment follow-up period. For patients that have entered the Extended Treatment Periods, study participation will be up to an additional 104 weeks or until commercialization of product, whichever is sooner	Edited length of Extended Treatment Period to allow patients in France to continue to receive study drug until commercialization of product.
Section 3.4.4 Post-Treatment Follow-Up	Section 3.4.4 The post-treatment follow-up period is at least 26 weeks and consists of at least 9 Study Center visits. For patients not continuing into the 52-week extended treatment period, the post-treatment follow-up period visits will be conducted on Weeks 53, 54, 55, 56, 57, 58, 65, 71, and 78 (Weeks 53, 54, 55, 56, 57, 58, and 71 may be conducted by a home healthcare nurse). For patients who have entered the first 52-week extended treatment period, but will not continue into the second 52-weeks of the extended treatment period, the post-treatment follow-up period visits will be conducted on Weeks 105, 106, 107, 108, 109, 110, 117, 123 and 130 (Weeks 105, 106, 107, 108, 109, 110 and 123 may be conducted by a home healthcare nurse). For patients who have entered the second 52-week extended treatment period, the post-treatment follow-up period visits will be on Weeks 157, 158, 159, 160, 161, 162, 169, 175 and 182 (Weeks 157, 158, 159, 160, 161, 162 and 175 may be conducted by a home healthcare nurse). Section 6.1.5	Added details of follow-up period for the first and second Extended Treatment Periods.

Section 6.1.5 Post-Treatment Follow-Up	After completion of the Week 52 visit assessments, patients will have the option of continuing ~~dosing~~ treatment for up to an additional ~~52~~104 weeks as described in Section 6.1.3. Patients not continuing ~~dosing~~ treatment will enter the 26-week post treatment follow-up. ~~The 26~~For patients not continuing into the 52-week extended treatment period, the 26-week post-treatment follow-up period consists of at least 9 Study Center visits on Weeks 53, 54, 55, 56, 57, 58, 65, 71, and 78 (Weeks 53, 54, 55, 56, 57, 58, and 71 may be conducted by a home healthcare nurse). ~~An additional 26~~ For patients who enter the first 52-week ~~post treatment follow-up occurs after~~extended treatment period, but will not continue into the second 52-weeks of the extended treatment period ~~with at least 9 Study Center~~, the post-treatment follow-up period visits will be conducted on Weeks 105, 106, 107, 108, 109, 110, 117, ~~118,~~123 and ~~125~~130 (Weeks 105, 106, 107, 108, 109, 110 and ~~118~~123 may be conducted by a home healthcare nurse). For patients who enter the second 52-week extended treatment period, the post-treatment follow-up period visits will be on Weeks 157, 158, 159, 160, 161, 162, 169, 175 and 182 (Weeks 157, 158, 159, 160, 161, 162 and 175 may be conducted by a home healthcare nurse).	
Section 5.2 Exclusion Criteria Synopsis, Study Population	14. Use of any of the following: … c. Systemic corticosteroids or anabolic steroids within 6 weeks prior to Qualification ~~unless approved by the Sponsor Medical Monitor~~ … 16. Known hypersensitivity to any of the excipients of the Study Drug (ISIS 304801 ~~or placebo~~)	Exceptions to inclusion or exclusion criteria will not be granted.
Section 6.1.3 Extended Treatment Period	Blood sampling will be conducted weekly ~~at Weeks 53, 54, 55, 56, 57, 58, 59, 60, 61, 62,63, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102,~~ and ~~103~~ may be conducted by a home healthcare nurse	Modified to indicate that blood sampling will occur weekly for increased clarity and to include an up to 104 additional weeks of extended treatment.
Section 6.2.1 Laboratory Assessments Section 8.5.4 Safety Monitoring for Constitutional Symptoms	Should a patient experience constitutional or flu-like symptoms after Study Drug administration, investigators may consider additional laboratory assessments. For example, plasma and serum samples may be drawn for complement (Total C3, C4, C5a and Bb), high-sensitivity C-reactive protein (hsCRP) and for cytokine analysis.	To add additional laboratory assessments permitted for safety purposes.

Section 6.2.4 ECG	Patients in the Extended Treatment Periods will have ECGs performed in triplicate at Weeks 76 and, 104~~. and 130~~. Triplicate ECGs will be performed at Weeks 13 and 26 of each post-treatment follow-up period.	To detail additional ECG assessments in the post-treatment follow-up period.
Section 6.2.6 Quality of Life Assessments	Should the patient enter the extended treatment periods, ~~A~~additional Quality of Life Questionnaires will be collected at Weeks ~~17~~13 and ~~130~~ 26 of each ~~should the patient enter the extended treatment period~~ post-treatment follow- up period.	To detail additional QoL assessments in the post-treatment follow-up period.
Section 8.1 Volanesorsen Administration	For each individual patient, volanesorsen will be administered subcutaneously as a single 1.5 mL 300 mg injection once weekly for Weeks 1-52. Patients entering this ISIS 304801-CS7 study on a reduced dose or dose frequency of Study Drug (volanesorsen), for safety or tolerability reasons in their index study (ISIS 304801-CS6 or ISIS 304801-CS16), will continue to receive study drug as a single 300 mg/1.5 mL injection once-weekly for Weeks 53-156~~104 receive a reduced dose or dose frequency of volanesorsen for continued safety or tolerability~~ as outlined in Sections 8.5 and 8.6. Patients on dose reduction will receive 300 mg/1.5 mL injections every 2 weeks ~~entering this CS7 study having dose or dose frequency reduced in the CS16 index study after 13 weeks of treatment, as outlined in CS16 Amendment 4 Section 8.7, can receive the 300 mg once weekly dose of volanesorsen.~~ Patients should receive 1 dose per week, unless on a dose reduction of 300 mg every 2 weeks, with weeks always defined relative to Study Day 1.	Added language clarifying details of dose reduction option as 300 mg every 2 weeks.
Section 8.5.2 Safety Monitoring for Platelet Count Results	Monitor every 1 week unless otherwise specified. In addition, platelet function may be evaluated at any time during the study by aggregometry, using an approved point-of-care diagnostic device, in some patients. This additional functional testing may be performed at selected study centers. … Due to the 1 to 3~~2~~-year study duration it is anticipated that patients may undertake travel including vacations, which may impede weekly platelet monitoring. In some situations, it may be possible to arrange for local laboratory testing or use of the home healthcare service at their temporary location. The intent is to maintain weekly platelet monitoring and ~~dosing~~ treatment where possible, as well as Investigator site contact with the study patients. However, if the above options are not possible, a temporary interruption of study treatment will be planned with a platelet count drawn within 3-5 days prior to departure and with a prompt blood draw upon the patient's return which must be reported and reviewed by the Investigator prior to the patient resuming ~~dosing~~ treatment.	Additional point-of-care platelet function testing may be conducted on patients at participating study centers. Included an additional blood draw to assess platelet count prior to any travel that would result in missing a weekly monitoring visit.

<table>
<tr><td></td><td colspan="3">Patients on dose pause should be monitored as per the platelet monitoring rules outlined in Section 8.8.1 until Study Drug administration is resumed.</td><td></td></tr>
<tr><td>Section 8.6.3 Stopping Rules for Platelet Count Results</td><td colspan="3">Table 3 Actions in Patients with Low Platelet Count
<table><tr><th>Platelet Count on Rx</th><th>Drug Dose</th><th>Monitoring</th></tr><tr><td></td><td>Study Drug administration is contingent on the availability of the immediately preceding test result. An interpretable platelet value must be available within 7 days prior to ~~dosing~~ treatment. Only the study doctor or qualified designee can authorize continued Study Drug administration based on an acceptable platelet value. Patients should not administer a dose until they have been contacted by their study doctor or designee and told that it is acceptable to dose. Authorization to dose must be documented in the patient's medical records.</td><td>Monitor every 1 week unless otherwise specified
In addition, platelet function may be evaluated during the study by aggregometry, using an approved point- of-care diagnostic device, in some patients. This additional functional testing may be performed at selected study centers.

Patients on dose pause should be monitored as per the platelet monitoring rules outlined in Section 8.8.1 until Study Drug administration is resumed.

Obtain additional lab tests (Table 2) if 2 occurrences (consecutive or non-consecutive) of platelet count 140K - > 100K/mm^3 or 1 occurrence of platelet count ≤ 100K/mm^3. Labs only need to be performed once. Labs may be collected over multiple visits, if blood requirements are a concern, as</td></tr></table></td><td>To provide clarification to the platelet safety monitoring rules, including dose reduction options.</td></tr>
</table>

			per Investigator discretion.
	> 100K/mm^3	Once ~~W~~weekly 300 mg Study Drug administration	
	100K/mm^3 - > 75K/mm^3	Permanently reduce dose frequency to 300 mg every 2 weeks.	
	75K/mm^3 - > 50K/mm^3	If occurs while on dose of 300 mg every 2 weeks, then permanently discontinue Study Drug, otherwise dose pause. If dose pause is ≥ 3 months then patient must discontinue treatment and enter the follow up period. When platelet count returns to > 100K/mm^3 restart ~~dosing~~ treatment at dose frequency of 300 mg every 2 weeks ~~only if approved by~~ in consultation with the Sponsor Medical Monitor	Monitor every 2-3 days until 2 successive values are > 75K/mm^3 then monitor every 1 week Consider discontinuation of antiplatelet agents/NSAIDS/ anticoagulant medication
	≤ 50K/mm^3 or a rate of decline ≥ 50% between two consecutive assessments, irrespective of the platelet level	Permanently discontinue Study Drug and the patient will enter the follow up period.	• Monitor daily until 2 successive values show improvement then monitor every 2-3 days until 2 successive values are > 75K/mm^3 then

				monitor every 1 week • Patient should be evaluated by a hematologist to provide diagnostic and therapeutic management • Steroids recommended*. It is strongly recommended that, unless the patient has a medical contraindication to receiving glucocorticoids, the patient receives glucocorticoid therapy to reverse the platelet decline. • Monitor triglyceride levels weekly and continue AE monitoring during steroid therapy • Discontinue antiplatelet agents/ NSAIDS/ anticoagulant medication while platelet count is < 50K/mm^3 if possible	
Section 8.7 Adjustment of Dose Frequency	Other dose adjustments, including dose interruptions, and/or decreasing the dose ~~or dose~~ frequency <u>to 300 mg every 2 weeks</u> will be allowed for safety and tolerability. Any proposed adjustment to treatment schedule must be discussed with, and approved by, the Study Medical Monitor prior to initiation. Up to 2 adjustments in the treatment schedule may be allowed. Patients may be dose paused in response to AEs ~~after consultation with~~<u>, and the</u> Study Medical Monitor <u>is informed. If a patient is dose paused for ≥ 3 months, he or she is considered to have discontinued treatment and should enter the 26-week post-treatment follow-up period</u>.				Clarification of dose reduction option to reduced dose frequency to allow for safety and tolerability Discontinuation of patients from the study who have been on dose pause and off study drug for >3 months.

Section 8.8 Discontinuation of Study Treatment	A patient must permanently discontinue study treatment for any of the following: … •<u>The patient is dose-paused for ≥ 3 months.</u>	Added new treatment discontinuation criterion consistent with other protocol changes.
Section 8.8.1 Follow-up Visits for Early Termination from Treatment Period	Any patient who discontinues early from the Treatment Period should be followed as per the platelet monitoring rules shown in Table 3 in Section 8.6.3 for the first 6 weeks after discontinuing Study Drug. Following this period, if the platelet count is stable (at least 3 consecutive values that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3), the next platelet count should be taken within at least 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug. ~~Patients should also be strongly encouraged to attend applicable landmark visits at Weeks 12, 13, 25, 26, and 50, 52 (calculated based on the time elapsed since Day 1) to collect fasting lipid panels and conduct safety assessments in accordance with the Schedule of Procedures in Appendix A.~~ Any patient who discontinues treatment after Week 44 should also be strongly encouraged to attend a final follow-up visit (Week 78 visit assessments) approximately 26 weeks after their last dose of Study Drug. ~~in addition to the applicable landmark visits.~~ <u>A patient who discontinues early from treatment with stable platelet counts above the LLN at the time of treatment discontinuation will have platelet counts drawn every 2 weeks after discontinuing Study Drug for the first 6 weeks after the last dose of Study Drug. A subsequent platelet count should then be taken after an additional 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug.</u>	Removal of language around landmark visits as patients who stop treatment now enter a post-treatment follow-up period Provides guidance for platelet monitoring in the post-treatment follow-up period.
Section 8.9 Withdrawal of Patient from the Study	Other reasons for withdrawal of patients from the study might include: • At the discretion of the Investigator for medical reasons • At the discretion of the Investigator or Sponsor for noncompliance • Significant protocol deviation • <u>Commercialization of product</u>	Added commercialization of product as an additional reason for withdrawal from study.
Section 8.10.2 Concomitant Procedures	Section 8.10.2 A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between signing of informed consent and Week 78 <u>(or Week 130 or 182 if the patient enters the first or second extended treatment period, respectively)</u> visit.	Updated to include follow-up period for the first and second Extended Treatment Periods.

Section 9.4.1 Serious Adverse Events Section 9.4.2 Non-Serious Adverse Events	Section 9.4.1 The collection of SAEs will begin after the patient signs the informed consent form and stop at the end of the patient's follow-up period which is defined as the Week 78 (or Week 130 or 182 if the patient enters the first or second extended treatment period, respectively) visit. Section 9.4.2 The recording of non-serious AEs will begin after the patient signs the informed consent form and will stop at the end of the patient's follow-up period, which is defined as the Week 78 (or Week 130 or 182 if the patient enters the first or second extended treatment period, respectively) visit.	
Section 13 REFERENCES	Gaudet D, Baass A, Tremblay K, et al. Natural History (up to 15 years) of Platelet Count in 84 Patients with Familial Hyperchylomicronemia Due to Lipoprotein Lipase Deficiency. Journal of Clinical Lipidology 2017; 11(3): 797-798.	Addition of reference
Section 14. APPENDICES	Appendix A Schedule of Procedures The following footnotes have been added to the tables for both the qualification through treatment period and the post-treatment follow-up period. g Genetic testing can be conducted for study Qualification (Group 2 ISIS 304801-CS16 roll over patients); genetic testing will only be conducted if allowed in the geographic region and only after the patient has given specific written informed consent for genetic testing. A blood sample for potential gene sequencing may be collected at timepoints other than Screening or Qualification Visits. The table for the first 52-week extended treatment period and post-treatment follow-up period have been defined and additional tables added for the second 52-weekextended treatment period and post-treatment follow-up period. Also added platelet function analysis to the first extended treatment period. With Footnote g May be done	Clarification that blood sampling for gene sequencing may occur during the study. Added an additional year of extended treatment Indication that platelet function may be assessed.
Section 14. APPENDICES	Appendix B List of Laboratory Analytes Platelet Function Platelet aggregation[3] Platelet function[5] Footnote 5: May be done using a point-of-care device on site.	Addition of laboratory analyte to measure platelet function.

Section 14. APPENDICES	Appendix C Pharmacokinetic Sampling Schedule Expanded PK Sampling Schedule to include timepoint for the First and Second 52-Week Extended Treatment Periods.	Addition of PK sampling timepoints for additional year of extended treatment.

PROTOCOL SYNOPSIS

Protocol Title	An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Study Phase	3
Indication	Familial Chylomicronemia Syndrome
Study Objectives	To evaluate the safety and efficacy of treatment and extended treatment with volanesorsen in patients with FCS
Study Design	This is a multi-center open-label study of: Group 1: ISIS 304801-CS6 (index study) roll over FCS patients Group 2: ISIS 304801-CS16 (index study) roll over FCS patients All patients will receive volanesorsen 300 mg once per week for 52 weeks. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period. Following the Week 52 visit, patients will have the option to continue treatment for up to an additional 104 weeks for a total of up to 156 weeks of treatment. Patients not continuing treatment will enter a 26-week post-treatment follow-up period.
Number of Patients	Up to approximately 70 patients dosed
Study Population	Inclusion Criteria: 1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law 2. Age ≥ 18 years at time of informed consent 3. Groups 1 and 2: Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement. Group 2: Patients who enrolled in ISIS 304801-CS16 must also meet the following criteria in order to enter into the open-label study: a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L) b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) supported by documentation of at least 1 of the following: • Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as lipoprotein lipase [LPL], apoC-II, GPIHBP1, or lipase maturation factor [LMF1]) • Post heparin plasma LPL activity of ≤ 20% of normal in medical history. Note: testing of LPL activity should not be performed to confirm eligibility for the study c. Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 index study

PROTOCOL SYNOPSIS Continued

Study Population *Continued*	Inclusion Criteria: *Continued* 4. Able and willing to participate in a 78-week study5. Satisfy 1 of the following: a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and follicle stimulating hormone (FSH) levels in the postmenopausal range for the laboratory involved), abstinent*, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration b. Males: Surgically sterile, abstinent* or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration * Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception Exclusion Criteria: 1. Diabetes mellitus with any of the following: a. Newly diagnosed within 12 weeks of Qualification b. HbA1c ≥ 9.0% at Qualification c. Recent change in anti-diabetic pharmacotherapy (change in dosage or addition of new medication within 12 weeks of Qualification [with the exception of ± 10 units of insulin]) d. Anticipated need to change dose or type of medication during the treatment period of the Study (with the exception of ± 10 units of insulin) e. Current use of glucagon-like peptide-1 (GLP-1) agonists 2. Severe hypertriglyceridemia other than due to familial chylomicronemia syndrome 3. Active pancreatitis within 4 weeks prior to Qualification 4. History within 6 months of Qualification of acute or unstable cardiac ischemia (myocardial infarction, acute coronary syndrome, new onset angina), stroke, transient ischemic attack or unstable congestive cardiac failure requiring a change in medication or major surgery within 3 months of Qualification

PROTOCOL SYNOPSIS Continued

Study Population *Continued*	Exclusion Criteria: *Continued* 5. Any of the following laboratory values at Qualification a. Hepatic: • Total bilirubin > upper limit of normal (ULN), unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL • ALT > 2.0 x ULN • AST > 2.0 x ULN b. Renal: • Persistently positive (2 out of 3 consecutive tests ≥ 1+) for protein on urine dipstick. In the event of a positive test eligibility may be confirmed by a quantitative total urine protein measurement of < 500 mg/24 hrs • Persistently positive (2 out of 3 consecutive tests ≥ trace positive) for blood on urine dipstick. In the event of a positive test eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field • Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault < 50 mL/min (MDRD or CKD-EPI formulas can be used instead of Cockcroft-Gault for estimation of glomerular filtration rate (GFR) in patients with low body weight after discussion with Sponsor Medical Monitor) c. Cardiac Troponin I > ULN at Qualification d. LDL-C > 130 mg/dL at Qualification e. Any other laboratory abnormalities which, in the opinion of the Investigator or the Sponsor, would make the patient unsuitable for inclusion 6. Uncontrolled hypertension (BP > 160/100 mm Hg) 7. History of thrombocytopenia (platelet count < 100,000/mm^3) or bleeding diathesis or coagulopathy or clinically-significant abnormality in coagulation parameters at Qualification 8. History of heart failure with NYHA greater than Class II 9. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1 10. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B 11. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated 12. Treatment with another investigational drug, biological agent, or device within 1 month of Qualification, or 5 half-lives of investigational agent, whichever is longer 13. Unwilling to comply with lifestyle requirements (Section 6.3)

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	Exclusion Criteria: *Continued* 14. Use of any of the following: a. Statins, omega-3 fatty acids (prescription and over-the-counter [OTC]), or fibrates unless on a stable dose for at least 3 months prior to Qualification and dose and regimen expected to remain constant during the treatment period. Patients taking OTC omega-3 fatty acids should make every effort to remain on the same brand throughout the study b. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to Qualification c. Systemic corticosteroids or anabolic steroids within 6 weeks prior to Qualification d. Atypical antipsychotic medications (e.g., olanzapine and clozapine) unless on a stable dose for at least 3 months prior to Qualification and dose and regimen expected to remain stable throughout the study e. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to Qualification and dose and regimen expected to remain constant during the treatment period f. Glybera gene therapy within 2 years prior to Qualification g. Oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, and apixaban) unless on a stable dose for at least 4 weeks prior to Qualification and regular clinical monitoring is performed h. Tamoxifen, estrogens or progestins unless on a stable dose for at least 4 months prior to Qualification and dose and regimen expected to remain constant during the treatment period i. Plasma apheresis within 4 weeks prior to Qualification or planned during the study j. Prior exposure to ISIS 304801 k. Any other medication unless stable at least 4 weeks prior to Qualification (Occasional or intermittent use of over-the-counter medications will be allowed at Investigator's discretion) 15. Blood donation of 50 to 499 mL within 30 days of Qualification or of > 499 mL within 60 days of Qualification 16. Known hypersensitivity to any of the excipients of the Study Drug (ISIS 304801) 17. Have any other conditions, including new or worsening of existing condition, which, in the opinion of the Investigator or the Sponsor would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the study
Treatment Group	Volanesorsen 300 mg once per week
Study Drug Administration	Volanesorsen will be administered as subcutaneous (SC) injections.
Dose Adjustments	Dose adjustments, including dose interruptions and/or decreasing the dose frequency will be allowed for safety or tolerability after consultation with the Sponsor Medical Monitor.

PROTOCOL SYNOPSIS Continued

Rationale for Dose and Schedule Selection	The dose of 300 mg once weekly was chosen for the double-blinded placebo-controlled Phase 3 index studies (ISIS 304801-CS6 and ISIS 304801-CS16) based on the pharmacodynamic and safety analysis of the Phase 2 studies (Section 2.4) which included a subset of patients with FCS. The same dose of 300 mg once weekly will be used in this open-label study of FCS patients.

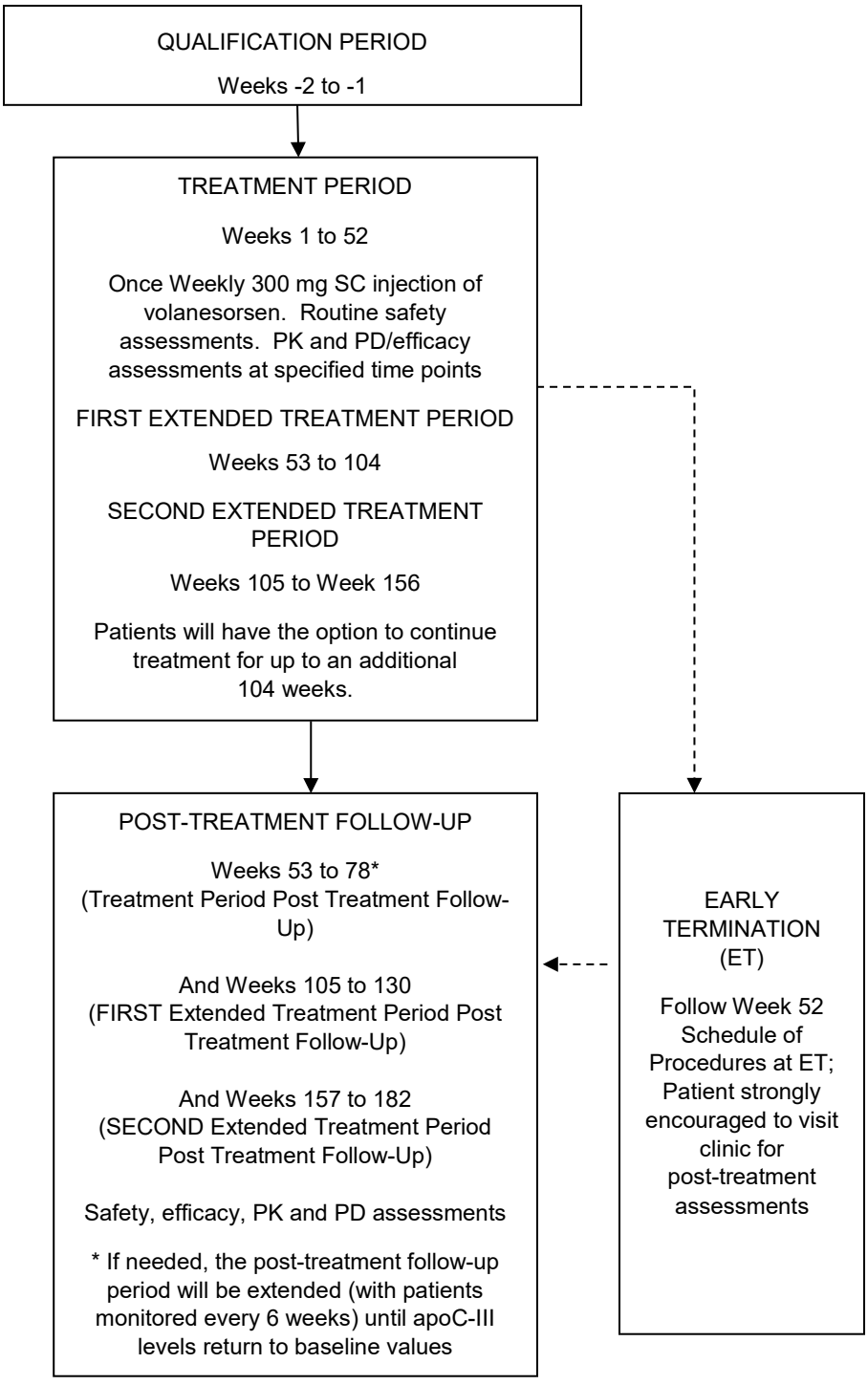
Study Visit Schedule and Procedures	The study for an individual patient will generally consist of the following periods:
	• A qualification period of up to 2 weeks (unless approved by the Sponsor). Please refer to Section 4.1 and Appendix A
	  ○ A 52-week treatment period during which volanesorsen will be administered as a once weekly SC injection
	  ○ Option to participate in an extended treatment period (up to an additional 104 weeks)
	  ○ A 26-week post-treatment follow-up period
	The patients, Investigators, study staff, and the Sponsor will remain blinded to lipid data through the last patient's Week 13 visit of the open-label study or until results from the database locks for the ISIS 304801-CS6 and ISIS 304801-CS16 index studies becomes available, whichever comes first.
	Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), adverse events (AE), concomitant medication/procedure information, lipid panel, blood viscosity, volanesorsen plasma concentrations, immunogenicity (IM) testing, platelet aggregation, liver/spleen magnetic resonance imaging (MRI), electrocardiograms (ECGs), echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Dietary counseling will be repeated at intervals throughout the treatment and follow-up period and a daily food/drink diary will be completed for the week prior to each quarterly visit by each patient. Following the Week 52 visit, patients will have the option to continue treatment for up to an additional 104 weeks. Patients not to continuing treatment will enter a 26-week post-treatment follow-up period.

Safety and Tolerability Evaluations	Overall safety and tolerability of volanesorsen will be assessed by determining the incidence and severity of adverse and serious adverse events (including independently adjudicated events of acute pancreatitis and MACE), withdrawals due to adverse events, and changes in laboratory and other safety parameters.

PROTOCOL SYNOPSIS Continued

Planned Analyses	Safety Endpoints: • Adverse events including adjudicated events of acute pancreatitis and MACE • Vital signs and weight • Physical examinations • Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis) • Echocardiography • ECGs • Use of concomitant medications • MRIs • Platelet aggregation (may be evaluated) Efficacy Endpoints: • Percent change and absolute change from baseline in fasting TG • Frequency and severity of patient reported abdominal pain during the treatment period • Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-high-density lipoprotein-cholesterol (non-HDL-C), apolipoprotein B [apoB], high-density lipoprotein-cholesterol (HDL-C), apolipoprotein A-1 [apoA-1], very-low-density lipoprotein-cholesterol (VLDL-C), and LDL-C • Percent change from baseline in fasting total apolipoprotein C-III (apoC-III) • Change in blood viscosity (may be evaluated) • Quality of Life questionnaires (EQ-5D, SF-36) • Adjudicated acute pancreatitis event rate • Other symptoms: eruptive xanthoma, lipemia retinalis
Pharmacokinetic Evaluations	Plasma samples will be taken from all patients for the measurement of volanesorsen as follows: trough levels (pre-dose) throughout treatment and post-treatment levels during the post-treatment follow-up period. In a subset of patients, more frequent assessment of plasma concentrations of volanesorsen will be performed to determine volanesorsen pharmacokinetic parameters. Plasma sample collection time points are detailed in Appendix A and Appendix C.
Statistical Considerations	No sample size calculations were performed as this is an open-label study.
Sponsor	Akcea Therapeutics, Inc.
Collaborator	Ionis Pharmaceuticals, Inc.

STUDY DESIGN AND TREATMENT SCHEMA



STUDY GLOSSARY

Abbreviation/Acronym	**Definition**
ADA	anti-drug antibody
AE	adverse Event
ALP	alkaline Phosphatase
ALT	alanine Aminotransferase
ANA	antinuclear Antibody
apoA-1	apolipoprotein A-1
apoB	apolipoprotein B
apoC-III	apolipoprotein C-III
apoE	apolipoprotein E
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
CBC	complete blood count
C_{max}	maximum observed drug concentration
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DNA	deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
ET	early termination
FAS	full analysis set
FCS	Familial Chylomicronemia Syndrome
FSH	follicle stimulating hormone
FPG	fasting plasma glucose
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
GPIHBP1	Glycosylphosphatidylinositol-anchored HDL-binding Protein 1
HAPI	Heritability and Phenotype Intervention
HbA1c	Glycated Hemoglobin
HDL	High-Density Lipoprotein
HDL-C	High-Density Lipoprotein-Cholesterol
hsCRP	High-sensitivity C-reactive protein
ICH	International Conference on Harmonization
IDL	Intermediate density lipoprotein

Abbreviation/Acronym	**Definition**
IEC	Independent Ethics Committee
IM	immunogenicity
Index Studies	ISIS 304801-CS6 and ISIS 304801-CS16
INR	International Normalized Ratio
IRB	Institutional Review Board
IXRS	Interactive Voice/Web-Response System
LDL	Low-Density Lipoprotein
LLN	Lower Limit of Normal
LDL-C	Low-Density Lipoprotein-Cholesterol
LMF1	Lipase Maturation Factor 1
LPL	Lipoprotein Lipase
MACE	Major Acute Cardiovascular Event
MedDRA	Medical Dictionary for Regulatory Activities
MOE	2′-*O*-(2-methoxyethyl)
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NCS	not clinically-significant
NOAEL	No-Observed-Adverse-Effect Level
non-HDL-C	Non-High-Density Lipoprotein-Cholesterol
OTC	over the counter
PFS	prefilled syringe
PD	pharmacodynamic
PK	pharmacokinetic
PPS	per protocol set
PT	prothrombin time
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SMPG	self-monitored plasma glucose
SUSAR	suspected unexpected serious adverse reaction
T2DM	type 2 diabetes mellitus
T_{max}	time to maximal concentration
TG	triglycerides
Treatment-emergent	occurring after first dose of Study Drug
TRL	Triglyceride-Rich Lipoproteins
ULN	upper limit of normal

Abbreviation/Acronym	**Definition**
VLDL	Very-Low-Density Lipoprotein
VLDL-C	Very-Low-Density Lipoprotein-Cholesterol
VLDL-TG	Lipoprotein-Triglyceride
WMA	World Medical Association

1. OBJECTIVES

The objective of the study is to evaluate the safety and efficacy of treatment and extended treatment with volanesorsen in patients with familial chylomicronemia syndrome.

2. BACKGROUND AND RATIONALE

2.1 Overview of Disease

Familial Chylomicronemia Syndrome (FCS) is an inherited disease characterized by severe hypertriglyceridemia and chylomicronemia, and risk or history of pancreatitis. It is a rare autosomal recessive disease that can be diagnosed either in childhood or adulthood.

Fasting plasma triglyceride (TG) levels in FCS patients are typically 10-fold to 100-fold above normal (1,500 to 15,000 mg/dL), despite extreme dietary fat restriction (20 g or approximately 15-20% of daily calorie intake) (Brunzell 1999-2011). Patients with FCS often present in infancy or childhood with frequent and severe abdominal pain, repetitive colicky pain, repeated episodes of potentially fatal acute pancreatitis, and failure to thrive (Brunzell 1999-2011; Tremblay et al. 2011). Physical examination frequently reveals eruptive xanthomas, lipemia retinalis and hepatosplenomegaly, and plasma from patients appears lactescent, interfering with determination of other laboratory parameters (Tremblay et al. 2011).

Patients with fasting triglyceride levels > 10 mmol/L probably have a component of chylomicronemia. Clinical diagnosis would include evidence of clinical features of chylomicronemia syndrome and secondary causes such as uncontrolled type 1 or type 2 diabetes mellitus (T2DM), hypothyroidism, poor diet, alcohol use, nephrotic syndrome or use of associated medications should be ruled out. The diagnosis of FCS may be made more specifically by genotyping or confirmation of very low or absent lipoprotein lipase (LPL) enzyme activity in post heparin plasma (Brunzell 1999-2011).

Patients with FCS carry a heavy burden of medical complications, the most serious, as described above, being an extreme risk of recurrent and potentially fatal pancreatitis. Due to the recurrent episodes of acute pancreatitis, these patients may also develop chronic pancreatitis and signs of exocrine or endocrine pancreatic insufficiency, including diabetes mellitus (Gaudet et al. 2013). While the pathophysiology underlying chylomicron-related pancreatitis has not been completely elucidated, 1 hypothesis is that large chylomicrons lodged in pancreatic capillaries are exposed to pancreatic lipase, with the subsequent release of free fatty acids through the hydrolysis of chylomicron-associated TGs. High concentrations of free fatty acids are thought to damage pancreatic cells leading to emergent pancreatitis (Yang et al. 2009; Berglund et al. 2012).

The etiology of extreme hypertriglyceridemia in FCS is considered to be ineffective triglyceride clearance, due to an extremely low level of LPL activity. LPL normally functions to hydrolyze triglycerides (TG) in chylomicrons along the luminal surface of capillaries, mainly in heart, skeletal muscle, and adipose tissue, promoting triglyceride clearance from the circulation. LPL is regulated by a number of key genes, and loss-of-function mutations in one of these genes, or the LPL gene itself, results in FCS (Surendran et al. 2012). In addition to loss of function mutations, null mutations, and nonsense mutations in the LPL gene, other genes currently identified in FCS patients, and known to directly influence LPL activity include: apolipoprotein C-II (APOC2) a cofactor for LPL (Schuster et al. 2011); apolipoprotein A-V (APOA5) an enhancer of LPL activity (Schaap et al. 2004); lipase maturation factor 1 (LMF1), a transmembrane protein involved in LPL maturation (Doolittle et al. 2009); glycosylphosphatidylinositol-anchored high-density lipoprotein (HDL)-binding protein 1 (GPIHBP1), a

capillary endothelial cell protein that provides a platform for LPL-mediated processing of chylomicrons (Beigneux et al. 2007).

2.2 Therapeutic Rationale

Apolipoprotein C-III (ApoC-III), a key regulator of plasma triglyceride levels, is a 79 amino acid glycoprotein synthesized principally in the liver (Ooi et al. 2008; Figure 1). ApoC-III is a major regulator of lipoprotein metabolism and plays a pivotal role in regulating plasma TG levels (Chan et al. 2008). It is a component of triglyceride-rich lipoproteins (TRLs) and a potent inhibitor of LPL (Lemieux et al. 2003). At higher concentrations apoC-III also inhibits hepatic lipase activity (Kinnunen and Ehnolm 1976), an enzyme which plays an important role in the conversion of dense very-low-density lipoprotein (VLDL) to intermediate density lipoprotein (IDL) and to LDL (Mendivil et al. 2010), as well as in the remodeling of HDL (Brown et al. 2010). In addition, increased apoC-III content adversely affects apolipoprotein E (apoE)-mediated hepatic uptake of TG-rich remnants (Mann et al. 1997). Thus, elevated plasma apoC-III levels are associated with impaired hydrolysis and retarded clearance of TG-rich particles, resulting in the accumulation of lipoprotein-triglyceride (VLDL-TG) and chylomicrons in plasma and the development of hypertriglyceridemia (Ito et al. 1990).

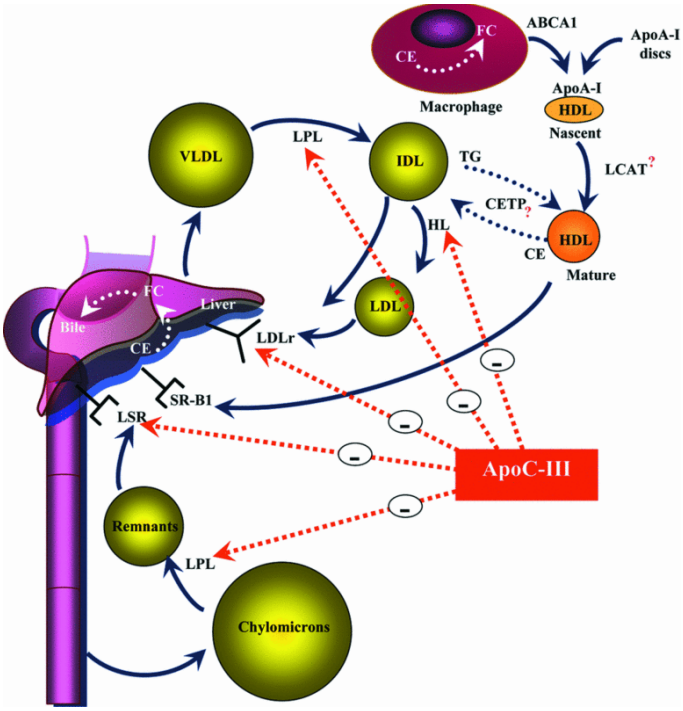


Figure 1 ApoC-III Regulates Lipoprotein Metabolism by Multiple Mechanisms

From Ooi et al. 2008; ABCA1 = ATP-binding cassette A1, apo = apolipoprotein, CE = cholesterol ester, CETP = cholesterol ester transfer protein, FC = free cholesterol, HDL = high-density lipoprotein, HL = hepatic lipase, IDL = intermediate-density lipoprotein, LCAT = lecithin cholesterol acyltransferase, LDL = low-density lipoprotein, LDLr = LDL receptor, LPL = lipoprotein lipase, LSR = lipolysis-stimulated receptor, SR-B1 = scavenger receptor B-1, TG = triglyceride, VLDL = very low-density lipoprotein.

Mechanistically, FCS is primarily a consequence of ineffective clearance of TRL. ApoC-III is a prominent component of TRL (e.g., VLDL and chylomicrons). In addition to its role in inhibiting LPL,

apoC-III inhibits TRL remnant (TG-depleted remnant lipoprotein) uptake by hepatic lipoprotein receptors by steric inhibition of the interaction of apoE with these receptors.

Human genetic data have demonstrated positive phenotypic associations with loss (e.g., null or nonsense mutations) and negative effects with gain of function mutations (Atzmon et al. 2006; Pollin et al. 2008; Petersen et al. 2010). A novel nonsense mutation in the apoC-III gene was identified in the heritability and phenotype intervention (HAPI) heart study in Old Order Amish that results in lower plasma apoC-III and TG levels and lower low-density lipoprotein-cholesterol (LDL-C), increased HDL-C and reduced atherosclerosis (Pollin et al. 2008). In another study involving a group of 214 Ashkenazi Jews of advanced age (had passed or nearly reached 100 years of age), genotype analysis revealed a polymorphism in the apoC-III gene (APOC3-641CC genotype) with a clear pattern of age-dependent frequency that was associated with significantly lower levels of apoC-III protein, a favorable lipoprotein profile and increased longevity (Atzmon et al. 2006). In contrast to the Amish and Ashkenazi apoC-III polymorphisms associated with lower plasma TG, apoC-III polymorphisms associated with higher plasma TG have also been recently described (Petersen et al. 2010). In a cohort of lean (mean body mass index [BMI] = 24.7 ± 3.6 kg/m^2) Asian Indians, carriers of apoC-III variant alleles (C-482T, T-455C, or both) were noted to have significantly higher plasma apoC-III and TG levels, and decreased ability to clear postprandial plasma TG from the circulation. Taken together, the available data strongly support the development of a therapy that reduces plasma apoC-III levels in order to reduce the very high circulating triglyceride and chylomicron levels that are accompanied by increasing risk for acute pancreatitis.

Given the profound reductions in TGs observed with volanesorsen treatment in FCS patients who have no detectable LPL activity (See Section 2.3.4), and the mechanistic data available to date on apoC-III function, potential mechanisms that explain how apoC-III inhibition results in triglyceride reduction in FCS patients include: (1) enhancing the very small residual amounts of LPL activity that these patients may have, below the limit of detection of the assay in many cases (2) potentially enhanced activity of other lipases also involved in the metabolism and breakdown of TGs, such as hepatic lipase or endothelial lipase (Kinnunen and Ehnolm 1976), and (3) apoC-III interaction with Apolipoprotein E (apoE), an important factor in liver reuptake of lipid particles by blocking apoE-mediated uptake of lipid particles in the liver (Breyer et al. 1999), and therefore, reducing apoC-III might enhance apoE-mediated uptake of lipid particles. Volanesorsen-mediated reduction of apoC-III could be contributing to one or all of these mechanisms resulting in the observed potent and sustained reductions in TG.

Through a novel apoC-III lowering mechanism of action, volanesorsen may provide the potential to manage triglyceride levels in FCS patients.

2.3 Volanesorsen

2.3.1 Mechanism of Action

Volanesorsen is a second-generation antisense oligonucleotide (ASO) drug targeted to human apoC-III. It is complementary to a region within the 3′ untranslated region of the apoC-III messenger ribonucleic acid (mRNA) and binds to the mRNA by Watson and Crick base pairing. The hybridization (binding) of volanesorsen to the cognate mRNA, results in the RNase H1-mediated degradation of the apoC-III mRNA, thus preventing production of the apoC-III protein. Maximal antisense-mediated reduction of target mRNA levels is typically greater than 90% of control levels in sensitive tissues (Crooke and Bennett 1996; Zhang et al. 2010). Furthermore, reduction in target mRNA levels using this approach correlates directly with a subsequent reduction in target protein levels.

2.3.2 Chemistry

Chemically, volanesorsen is a synthetic oligomer of 20 nucleotides (i.e., a 20-mer) that are connected sequentially by phosphorothioate linkages. The nucleotide sequence of volanesorsen (Figure 2) is complementary to a 20-nucleotide stretch within the 3′ untranslated region of the apoC-III mRNA transcript at base position 489-508. Structurally, the oligonucleotide has 3 regions. Two (2) of them, the 5 nucleotides at the 5′ end and the 5 nucleotides at the 3′ end, are composed of 2′-*O*-(2-methoxyethyl) (MOE)-modified ribonucleotides. These MOE-modified nucleotides confer (1) increased affinity to the target mRNA (Altmann et al. 1996; McKay et al. 1999), (2) increased resistance to exonucleases and endonucleases (thereby increasing stability in tissue) (Geary et al. 2003), and (3) amelioration of some of the high dose toxicities thereby resulting in an improved safety profile compared to first generation antisense drugs containing phosphorothioate modified oligodeoxynucleotides (DNA) (Henry et al. 2000). The third region, the central portion of the oligonucleotide, is composed of 10 oligodeoxynucleotides. This chimeric design is called a MOE-Gapmer, and volanesorsen employs this chimeric structure to enable use of the RNase H1-mechanism for antisense activity. This is because while the 2′-MOE modification confers increased stability and affinity, it does not support RNase H1 catalysis of RNA hybridized to 2′-MOE-modified nucleotides (McKay et al. 1999). This is caused by conformational changes induced in the heteroduplex by 2′-alkoxy:RNA hybrids that are not recognized by RNase H1 enzymes (Inoue et al. 1987; Monia et al. 1993). By limiting the 2′-MOE modification to nucleotides flanking the phosphorothioate oligodeoxynucleotide core, the beneficial attributes of the 2′-MOE chemistry are preserved while also retaining RNase H1 recognition.

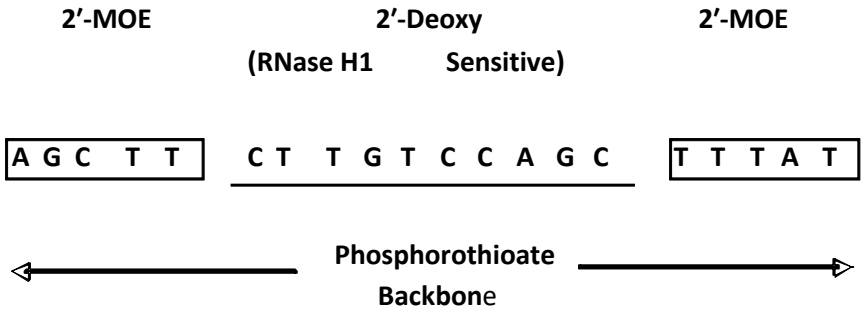


Figure 2 Design of Chimeric 2′-MOE Phosphorothioate Oligonucleotides (MOE-Gapmer). The sequence of volanesorsen is shown.

2.3.3 Preclinical Experience

Inhibition of apoC-III using volanesorsen has been shown to potently reduce hepatic apoC-III mRNA as well as plasma apoC-III protein and TG in a dose- and time-dependent fashion in several species, including human apoC-III transgenic mice, and other rodent and monkey models. Treatment with volanesorsen also resulted in reduced VLDL and chylomicron TG and reduced postprandial TG in hypertriglyceridemic monkeys (Graham et al. 2013).

The pharmacokinetics (PK) and toxicity of volanesorsen have been assessed in mice, rats, and cynomolgus monkeys. General toxicity studies with volanesorsen for up to 39 weeks of treatment followed by up to a 20-week recovery period are complete. The preclinical toxicology program for volanesorsen consists of single dose safety pharmacology studies in the monkey (cardiovascular) and

mouse (neurobehavioral and pulmonary assessment studies), *in vitro* and *in vivo* genetic toxicity assessment, repeat dose fertility and/or developmental reproductive toxicology studies in the mouse and rabbit and evaluation in the *in vitro* human Ether-á-go-go-related gene (hERG) assay.

Volanesorsen treatment-related findings in mice and monkeys were generally consistent with those expected for the 2′-MOE-class of ASOs. Treatment-related findings included effects consistent with drug accumulation in tissues in rodents and monkeys, species-dependent proinflammatory response in rodents and monkeys and complement activation and reductions in platelet counts in the monkey. In the mouse and monkey general toxicity studies, reduction of hepatic apoC-III mRNA (> 75%) was not associated with any findings that could be considered related to the pharmacologic inhibition of apoC-III for up to 39 weeks of treatment.

The long-term, chronic toxicology studies in rodents with volanesorsen produced a significant proinflammatory response that led to subsequent effects on the heart at high doses. The rodent species are most sensitive to the proinflammatory effects of antisense molecules. Importantly, these effects on the heart were not observed in the monkey chronic toxicity studies even at the highest doses tested where drug exposure was higher than that in rodents.

Because these changes were not observed in monkeys, the findings in the heart are considered to be rodent-specific and not relevant to humans. Nevertheless, such effects will be monitored by measurement of echocardiograms that will be included in this clinical study.

Volanesorsen caused no untoward effects in safety pharmacology studies (*in vitro* and *in vivo*) and was non-genotoxic (*in vitro* and *in vivo*). Volanesorsen had no effects on fertility or embryo/fetal development in the mouse or rabbit reproductive toxicity studies. In these studies, volanesorsen was detected in placental tissue but not in fetal tissue indicating that little, if any, drug was able to cross the placenta to reach the fetus. Reduction of apoC-III mRNA (64% in males and 47% in females) also did not affect fertility or cause untoward effects on embryo/fetal development in mice.

Detailed information concerning the preclinical studies conducted with volanesorsen can be found in the volanesorsen Investigator's Brochure.

2.3.4 Clinical Experience

Detailed information concerning the clinical studies conducted with volanesorsen can be found in the volanesorsen Investigator's Brochure. A summary is included below.

The clinical experience with volanesorsen includes clinical trials in healthy subjects, patients with hypertriglyceridemia, FCS, or familial partial lipodystrophy. Overall, 431 patients and healthy volunteers have taken part in the clinical development program, of whom 325 have received at least 1 dose of volanesorsen. Ninety-five (95) patients with FCS have been enrolled in studies, all showing clinically meaningful reductions in plasma triglyceride. Patients with FCS continue on treatment in the open-label extension (OLE) and triglyceride reductions persist at similar levels as reported in earlier studies.

In the completed Phase 1 and Phase 2 studies, volanesorsen was well-tolerated and demonstrated a favorable safety profile. There was no clinical or laboratory evidence of drug-drug interactions despite many patients in the Phase 2 clinical trials receiving concomitant medications that are known to be associated with elevations in hepatic enzymes, such as fibrates and statins. There were no volanesorsen-associated laboratory abnormalities suggestive of an effect on the renal (serum creatinine, proteinuria) or hepatic systems (alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin). There

was a reduction (mean reduction < 30%) in platelets in volanesorsen vs. placebo with mean nadirs for all doses remaining above the lower limit of normal (LLN). The most frequently reported adverse events (AEs) were mild, non-progressive events at the injection site. In Phase 2, a single serious adverse event (SAE) of secondary serum sickness-like reaction was reported as related to Study Drug.

All clinical trials of volanesorsen have shown large and clinically meaningful reductions in fasting plasma apoC-III and TG (~80% and 70%, respectively, mean reduction from baseline with 300 mg dose) with a very high degree of consistency of response between the different patient groups. This includes healthy volunteers, patients with moderate to severe hypertriglyceridemia not on background TG-lowering therapy, patients with moderate to severe hypertriglyceridemia on a background stable fibrate therapy (Gaudet et al. 2015), patients with FCS, and patients with T2DM. In a Phase 2 study, 3 patients with FCS were treated with 300 mg/wk volanesorsen in an open-label fashion. These patients had a mean baseline fasting TG level of 1,844 mg/dL and all 3 patients achieved TG levels below or close to 500 mg/dL during the treatment period out to Day 92 (Figure 3). Two (2) of the FCS patients had an absolute reduction in fasting TG in excess of 1,500 mg/dL (Gaudet et al. 2014).

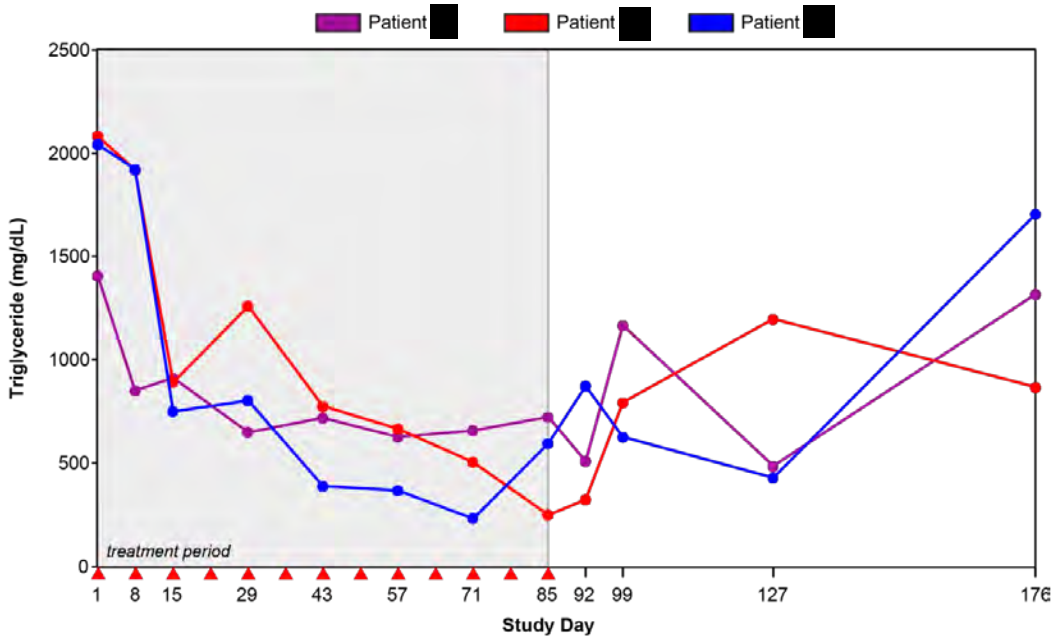


Figure 3 Fasting Triglycerides in Patients with FCS Treated with Volanesorsen

In the completed pooled Phase 3 studies (ISIS 304801-CS6 (hereafter referred to as CS6) and ISIS 304801-CS16 (hereafter referred to as CS16), the most common AEs associated with volanesorsen administration were tolerability at the injection site and platelet reductions. The majority of the injection site AEs were mild, none were severe, and the incidence appeared to decrease over time. No deaths have been associated with volanesorsen treatment to date. No cardiac toxicity was associated with volanesorsen treatment. There were no abnormal QTc findings and no study-drug related adjudicated major adverse cardiac events (MACE). There is no evident association between volanesorsen treatment and changes in renal or liver functions.

The safety profile of volanesorsen has been well-described in this development program, which has identified 3 safety risks: thrombocytopenia (an identified risk), constitutional symptoms (flu-like reactions and influenza-like illness), and injection site reactions (a tolerability signal). Spontaneous, mild-to-severe thrombocytopenia has been described in the FCS patient population (Gaudet et al. 2017) but is increased by treatment with volanesorsen. Less frequent and less pronounced platelet declines were also observed with volanesorsen treatment in the hypertriglyceridemic (HTG) population of CS16. When fully complied with, frequent monitoring for this effect and appropriate dose adjustments have been successful both in preventing and promptly detecting the occurrence of severe platelet declines and often in retaining patients on treatment.

2.4 Rationale for Dose and Schedule of Administration

The dose and schedule selected for this study is 300 mg per week for 52 weeks, with the option of continuing treatment for up to an additional 104 weeks. The dose of 300 mg per week and dose reduction of 300 mg every 2 weeks (delivered as a single 300 mg dose) are supported by both the cumulative nonclinical data available to date and the Phase 2 clinical data. In nonclinical studies, volanesorsen treatment-related effects in rodents and monkeys were consistent with drug accumulation in tissues and also include species-specific proinflammatory responses. In the monkey, the No-Observed-Adverse-Effect Level (NOAEL) was defined by the cumulative clinical pathology results and histopathology data which provide an adequate clinical margin. Non clinical findings were not considered to be related to the pharmacologic inhibition of apoC-III.

The safety data to date suggest that volanesorsen has been well-tolerated at dose levels up to 300 mg in patients with high triglycerides (including type 2 diabetes patients and administration in combination with fibrates and statins) with the most common AEs being local to the injection site and predominantly mild. A pooled analysis of safety for the Phase 2 studies did not demonstrate any clear difference in safety or tolerability between the different doses tested (100 mg, 200 mg, and 300 mg per week for 13 weeks).

Analysis of the cohorts in which volanesorsen was studied at different doses demonstrates dose-dependent pharmacology with respect to pharmacodynamic (PD) effect on the target, apoC-III, with a clear difference in the TG-lowering effect between the different doses in the 100 mg to 300 mg dose range as compared to placebo.

In addition to the nonclinical and clinical experience of volanesorsen, the dose and schedule of administration is supported by the preclinical and clinical safety experience of several other 2′-MOE-modified ASOs that have been administered intravenously and subcutaneously in multiple clinical studies at doses up to 1200 mg and for treatment durations that exceed 24 months (Santos et al. 2015).

3. EXPERIMENTAL PLAN

3.1 Study Design

This is an open-label study of:

Group 1: ISIS 304801-CS6 (index study) roll over FCS patients

Group 2: ISIS 304801-CS16 (index study) roll over FCS patients

Up to approximately 70 patients will receive 300 mg once weekly volanesorsen for 52 weeks.

Following the Week 52 visit, patients will have the option to continue treatment for up to an additional 104 weeks for a total of up to 156 weeks of treatment. Patients not continuing treatment will enter a 26-week post-treatment follow-up period.

3.2 Number of Study Centers

This study will be conducted at multiple centers worldwide.

3.3 Number of Patients

Up to approximately 70 patients will be dosed.

3.4 Overall Study Duration and Follow-up

The Study will consist of the following periods:

3.4.1 Qualification

A qualification period of up to 2 weeks (unless approved by the Sponsor) is given to complete qualification assessments outlined in the Schedule of Procedures. Please refer to Section 4.1 and Appendix A.

3.4.2 Treatment

The treatment period is 52 weeks. Eligible patients will report to the Study Center for assessments at specified intervals throughout the 52-week treatment period as detailed in the Schedule of Procedures (Appendix A). During the treatment period, volanesorsen is administered by subcutaneous (SC) injection once weekly.

3.4.3 Extended Treatment Period

After completion of the Week 52 visit assessments, patients will have the option of continuing treatment for up to an additional 104 weeks. Patients not continuing treatment will enter the 26-week post-treatment follow-up. For patients that have entered the Extended Treatment Periods, study participation will be up to an additional 104 weeks or until commercialization of product, whichever is sooner.

3.4.4 Post-Treatment Follow-Up

The post-treatment follow-up period is at least 26 weeks and consists of at least 9 Study Center visits. For patients not continuing into the 52-week extended treatment period, the post-treatment follow-up period visits will be conducted on Weeks 53, 54, 55, 56, 57, 58, 65, 71, and 78 (Weeks 53, 54, 55, 56, 57, 58, and 71 may be conducted by a home healthcare nurse).

For patients who have entered the first 52-week extended treatment period, but will not continue into the second 52-weeks of the extended treatment period, the post-treatment follow-up period visits will be conducted on Weeks 105, 106, 107, 108, 109, 110, 117, 123 and 130 (Weeks 105, 106, 107, 108, 109, 110 and 123 may be conducted by a home healthcare nurse).

For patients who have entered the second 52-week extended treatment period, the post-treatment follow-up period visits will be on Weeks 157, 158, 159, 160, 161, 162, 169, 175 and 182 (Weeks 157, 158, 159, 160, 161, 162 and 175 may be conducted by a home healthcare nurse).

3.5 End-of-Study

The End-of-Study is last patient, last visit.

3.6 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will review (as needed) safety, tolerability and efficacy data collected on volanesorsen during this study. Based on its ongoing assessment of the safety and tolerability of volanesorsen, the DSMB will provide recommendations to the Sponsor for modifying, stopping or continuing the study as planned. Details on the safety assessments, frequency of review and meeting schedules are outlined in the DSMB Charter and/or the statistical analysis plan (SAP).

4. PATIENT ENROLLMENT

4.1 Qualification

Before patients may be enrolled into the study, the Sponsor requires a copy of the Study Center's written independent ethics committee/institutional review board (IEC/IRB) approval of the protocol, informed consent form, and all other patient information.

Patients or their legally acceptable representatives must sign the consent form before any study-specific procedures or evaluations related to this open-label study are performed.

During the qualification period, the eligibility of the patient to enroll in the open-label study will be determined. Final assessments from the ISIS 304801-CS6 or ISIS 304801-CS16 studies may be used for qualification. A period of up to 2 weeks after completion of the ISIS 304801-CS6 or ISIS 304801-CS16 index studies (unless approved by the Sponsor) is given to complete qualification. Qualified patients will retain the unique patient identification number that was assigned to them during the ISIS 304801-CS6 or ISIS 304801-CS16 index studies. The patient identification number will be used to identify the patient throughout the extension trial and must be used on all study documentation related to that patient. The patient identification number must remain constant throughout the extension trial.

4.2 Enrollment

Patients will be enrolled into the treatment phase of the study after all qualification assessments have been completed and after the Investigator has verified that they are eligible per criteria in Sections 5.1 and 5.2. No patient may begin treatment prior to enrollment.

Eligible patients will be enrolled using an Interactive Voice/Web-Response System (IXRS).

5. PATIENT ELIGIBILITY

To be eligible to participate in this study candidates must meet the following eligibility criteria within 2 weeks of Study Day 1, or at the time point specified in the individual eligibility criterion listed.

5.1 Inclusion Criteria

1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law
2. Age ≥ 18 years at time of informed consent

3. Groups 1 and 2: Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement.

   Group 2: Patients who enrolled in ISIS 304801-CS16 must also meet the following criteria in order to enter into the open-label Study:

   a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L)

   b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) supported by documentation of at least 1 of the following:

      - Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1)
      - Post heparin plasma LPL activity of ≤ 20% of normal in medical history. Note: testing of LPL activity should not be performed to confirm eligibility for the study.

   c. Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 index study

4. Able and willing to participate in a 78-week study
5. Satisfy 1 of the following:

   a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and follicle stimulating hormone (FSH) levels in the postmenopausal range for the laboratory involved), abstinent*, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration.

   b. Males: Surgically sterile, abstinent* or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration.

   * Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception

5.2 Exclusion Criteria

1. Diabetes mellitus with any of the following:

   a. Newly diagnosed within 12 weeks of Qualification

   b. HbA1c ≥ 9.0% at Qualification

c. Recent change in anti-diabetic pharmacotherapy (change in dosage or addition of new medication within 12 weeks of Qualification [with the exception of ± 10 units of insulin])

d. Anticipated need to change dose or type of medication during the treatment period of the Study (with the exception of ± 10 units of insulin)

e. Current use of glucagon-like peptide-1 (GLP-1) agonists

2. Severe hypertriglyceridemia other than due to familial chylomicronemia syndrome

3. Active pancreatitis within 4 weeks prior to Qualification

4. History within 6 months of Qualification of acute or unstable cardiac ischemia (myocardial infarction, acute coronary syndrome, new onset angina), stroke, transient ischemic attack or unstable congestive cardiac failure requiring a change in medication or major surgery within 3 months of Qualification

5. Any of the following laboratory values at Qualification

a. Hepatic:

- Total bilirubin > upper limit of normal (ULN), unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL
- ALT > 2.0 x ULN
- AST > 2.0 x ULN

b. Renal:

- Persistently positive (2 out of 3 consecutive tests ≥ 1+) for protein on urine dipstick. In the event of a positive test eligibility may be confirmed by a quantitative total urine protein measurement of < 500 mg/24 hrs
- Persistently positive (2 out of 3 consecutive tests ≥ trace positive) for blood on urine dipstick. In the event of a positive test eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field
- Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault < 50 mL/min (MDRD or CKD-EPI formulas can be used instead of Cockcroft-Gault for estimation of glomerular filtration rate (GFR) in patients with low body weight after discussion with Sponsor Medical Monitor)

c. Cardiac Troponin I > ULN at Qualification

d. LDL-C > 130 mg/dL at Qualification

e. Any other laboratory abnormalities which, in the opinion of the Investigator or the Sponsor, would make the patient unsuitable for inclusion

6. Uncontrolled hypertension (BP > 160/100 mm Hg)

7. History of thrombocytopenia (platelet count < 100,000/mm^3) or bleeding diathesis or coagulopathy or clinically-significant abnormality in coagulation parameters at Qualification

8. History of heart failure with NYHA greater than Class II

9. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1
10. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B
11. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated
12. Treatment with another investigational drug, biological agent, or device within 1 month of Qualification, or 5 half-lives of investigational agent, whichever is longer
13. Unwilling to comply with lifestyle requirements (Section 6.3)
14. Use of any of the following:
    a. Statins, omega-3 fatty acids (prescription and over-the-counter [OTC]), or fibrates unless on a stable dose for at least 3 months prior to Qualification and dose and regimen expected to remain constant during the treatment period. Patients taking OTC omega-3 fatty acids should make every effort to remain on the same brand throughout the study
    b. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to Qualification
    c. Systemic corticosteroids or anabolic steroids within 6 weeks prior to Qualification
    d. Atypical antipsychotic medications (e.g., olanzapine and clozapine) unless on a stable dose for at least 3 months prior to Qualification and dose and regimen expected to remain stable throughout the study
    e. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to Qualification and dose and regimen expected to remain constant during the treatment period
    f. Glybera gene therapy within 2 years prior to Qualification
    g. Oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, and apixaban) unless on a stable dose for at least 4 weeks prior to Qualification and regular clinical monitoring is performed
    h. Tamoxifen, estrogens or progestins unless on a stable dose for at least 4 months prior to Qualification and dose and regimen expected to remain constant during the treatment period
    i. Plasma apheresis within 4 weeks prior to Qualification or planned during the study
    j. Prior exposure to ISIS 304801
    k. Any other medication unless stable at least 4 weeks prior to Qualification (Occasional or intermittent use of over-the-counter medications will be allowed at Investigator's discretion)
15. Blood donation of 50 to 499 mL within 30 days of Qualification or of > 499 mL within 60 days of Qualification
16. Known hypersensitivity to any of the excipients of the Study Drug (ISIS 304801)
17. Have any other conditions, including new or worsening of existing condition, which, in the opinion of the Investigator or the Sponsor would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the study

6. STUDY PROCEDURES

6.1 Study Schedule

All required study procedures are outlined in Appendices A, B, C, and D.

6.1.1 Qualification

Please refer to Section 4.1 and Appendix A.

6.1.2 Treatment Period

The patients, Investigators, study staff, and the Sponsor will remain blinded to lipid data through the last patient's Week 13 visit of the open-label study or until results from the database locks for the ISIS 304801-CS6 and ISIS 304801-CS16 index studies become available, whichever comes first.

During the treatment period, patients will report to the study center for clinic visits a minimum of 5 times during Weeks 1-52 (see Schedule of Procedures in Appendix A). Study Drug will be administered once weekly (Section 8.1). Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), AEs, concomitant medication/procedure information, lipid panel, blood viscosity, volanesorsen plasma concentrations, immunogenicity (IM) testing, platelet aggregation, liver/spleen magnetic resonance imaging (MRI), electrocardiograms (ECGs), echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Adverse events at the injection site should be collected as adverse events. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period and all patients will complete a daily food diary for one week prior to their quarterly visit. All blood and urine samples should be collected prior to volanesorsen administration. Blood sampling at Weeks 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, and 51 may be conducted by a home healthcare nurse. Approval for study procedures to be conducted by a home healthcare nurse on other outpatient visit days will require prior approval by the Sponsor. Patients must be fasted prior to drawing all blood samples and samples drawn locally should also be sent to the central laboratory for analysis whenever possible. Dosing instructions and training will be provided to the patient where applicable.

All reasonable attempts should be made to ensure compliance with the visit schedule as outlined in Appendix A. However, in the event that a visit does not occur or is delayed, all subsequent visits should be calculated based on the time elapsed since Day 1 rather than from the date of the previous visit.

6.1.3 Extended Treatment Period

After completion of the Week 52 visit assessments, patients will have the option of continuing treatment for up to an additional 104 weeks. For patients that have entered the Extended Treatment Periods, study participation will be up to an additional 104 weeks or until commercialization of product, whichever is sooner.

During the extended treatment period, patients will have assessments and procedures done during Weeks 54-156 as per the Schedule of Procedures in Appendix A. Assessments and procedures may be conducted by either a home healthcare service or the Study Center, however the patient will be required to visit the study center approximately every 3 months. Study Drug will be administered once weekly unless the patient is on a biweekly treatment schedule for safety reasons (Section 8.1). Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis),

AEs, concomitant medication/procedure information, lipid panel, volanesorsen plasma concentrations, IM testing, ECGs, and physical examinations will be performed according to the Schedule of Procedures in Appendix A. Adverse events at the injection site should be collected as adverse events. Dietary counseling will be reinforced at intervals throughout the extended treatment period. All blood and urine samples should be collected prior to volanesorsen administration. Blood sampling will be conducted weekly and may be conducted by a home healthcare nurse. Approval for study procedures to be conducted by a home healthcare nurse on other outpatient visit days will require prior approval by the Sponsor. Patients must be fasted prior to drawing all blood samples and samples drawn locally should also be sent to the central laboratory for analysis whenever possible. Treatment instructions and training will be provided to the patient where applicable.

6.1.4 Pharmacokinetic (PK) Subgroup

A subgroup of patients will participate in an extended PK collection. Patients in this subgroup will have more frequent PK sampling over a 24-hour period following the first dose on Study Day 1 in order to evaluate the plasma PK parameters of volanesorsen. Patients in this subgroup will have an additional visit to the clinic, or by a home healthcare nurse, on Day 2 to collect a 24-hour post-dose blood draw after treatment on Day 1. The detailed PK sampling schedules are outlined in Appendix C.

Participation in the PK subgroup is optional for sites and patients, and consent may be withdrawn for the subgroup-specific procedures (e.g., multiple blood draws for PK) without being withdrawn from the study. If a patient withdraws consent from the subgroup procedures, he/she should remain on study and continue to follow all the non-subgroup assessments and procedures as outlined in Appendix A.

6.1.5 Post-Treatment Follow-up

After completion of the Week 52 visit assessments, patients will have the option of continuing treatment for up to an additional 104 weeks as described in Section 6.1.3. Patients not continuing treatment will enter the 26-week post-treatment follow-up. For patients not continuing into the 52-week extended treatment period, the 26-week post-treatment follow-up period consists of at least 9 Study Center visits on Weeks 53, 54, 55, 56, 57, 58, 65, 71, and 78 (Weeks 53, 54, 55, 56, 57, 58, and 71 may be conducted by a home healthcare nurse).

For patients who enter the first 52-week extended treatment period, but will not continue into the second 52-weeks of the extended treatment period, the post-treatment follow-up period visits will be conducted on Weeks 105, 106, 107, 108, 109, 110, 117, 123 and 130 (Weeks 105, 106, 107, 108, 109, 110 and 123 may be conducted by a home healthcare nurse).

For patients who enter the second 52-week extended treatment period, the post-treatment follow-up period visits will be on Weeks 157, 158, 159, 160, 161, 162, 169, 175 and 182 (Weeks 157, 158, 159, 160, 161, 162 and 175 may be conducted by a home healthcare nurse).

These visits are outlined in the Schedule of Procedures in Appendix A.

6.2 Additional Study Assessments

6.2.1 Laboratory Assessments

Laboratory analyte samples will be collected throughout the study. A list of these analytes is contained in Appendix B.

Each time a hematology lab is drawn and sent to the central laboratory for analysis, an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples), another sample must be repeated within 1 week and the result must be reviewed by the Investigator and confirmed to be acceptable before treatment can continue. All platelet count results will be promptly reviewed by the Investigator to determine if the count has met a stopping rule, or the dose reduction rule of 100,000/mm^3, or the dose pause rule of 75,000/mm^3.

Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor.

Should a patient experience constitutional or flu-like symptoms after Study Drug administration, investigators may consider additional laboratory assessments. For example, plasma and serum samples may be drawn for complement (Total C3, C4, C5a and Bb), high-sensitivity C-reactive protein (hsCRP) and for cytokine analysis.

6.2.2 Physical Exams and Vital Signs

Physical exams and vital signs will be performed as indicated in the Schedule of Procedures (Appendix A). Vital signs should include weight, blood pressure, pulse rate, respiratory rate and body temperature. Blood pressure and pulse rate will be recorded after the patient has been in a sitting position for at least 5 minutes. Semi-supine systolic and diastolic blood pressure should always be measured on the same arm (preferentially on the left arm). Height will be measured at the Day 1 visit.

6.2.2.1 Eruptive Xanthoma

At each visit, patients will be asked whether they have had any episodes of eruptive xanthoma since their last visit and the number/duration of the events will be recorded. Physical exams should also include skin examination for presence/resolution of eruptive xanthomas. If a patient experiences an episode of eruptive xanthoma during the study, photos of the area should be taken, if possible.

6.2.2.2 Lipemia Retinalis

If possible, lipemia retinalis will be assessed by fundus photography prior to administration of the first dose of Study Drug (for ISIS 304801-CS16 roll over patients) and repeated at Week 52. Images will be evaluated by an independent assessor, blinded to the patient's treatment assignment.

6.2.3 Echocardiography

Echocardiography for assessment of left and right ventricular function and mitral and aortic valve function will be conducted at Week 26 and Week 52 in all patients. For the purpose of assessment of treatment-emergent changes, all echocardiograms will be evaluated on an ongoing basis by an independent central reader. Results will be provided to the DSMB for their review.

6.2.4 ECG

The ECG will be recorded after the patient has been resting in a supine position for at least 5 minutes. ECGs will be performed in triplicate at Week 13, Week 26, Week 38, Week 52. During the post-treatment follow-up, ECGs will be performed in triplicate at Weeks 65 and 78 for patients not opting to participate in the Extended Treatment Period. Patients in the Extended Treatment Periods will have ECGs performed in triplicate at Weeks 76 and 104. Triplicate ECGs will be performed at Weeks 13 and 26 of each post-treatment follow-up period.

6.2.5 MRI

MRI of the liver and spleen will be conducted at Week 52 for all patients for whom MRI is not contraindicated, e.g., patients having metal implants.

MRIs will be conducted using standardized procedures and settings. MRIs will be read by an independent central reader to assess liver fat and liver and spleen size**.**

6.2.6 Quality of Life Assessments

All patients will complete Quality of Life Questionnaires (EQ-5D and SF-36) at Week 1, Week 13, Week 26, and Week 52. During the post-treatment follow-up, patients will complete an EQ-5D and SF-36 during Weeks 65 and 78. Should the patient enter the extended treatment periods, additional Quality of Life Questionnaires will be collected at Weeks 13 and 26 of each post-treatment follow-up period.

6.2.7 Disease Symptom Diary

All patients will complete a symptom questionnaire once a week starting at the beginning of the qualification period and continuing to the end of the post-treatment follow-up period.

6.2.8 Diet Monitoring

The diets of patients enrolled in the study will be monitored as follows:

1. All patients will be required to maintain a 7-day food diary prior to Week 1, Week 13, Week 26, Week 52. During the post-treatment follow-up, patients will complete a 7-day food diary prior to Weeks 65 and 78.
2. Patients will receive diet/alcohol counseling by qualified study personnel at clinic visits throughout the course of the study. Qualified study personnel will telephone the patient to provide diet/alcohol counseling for visits that are conducted by a clinical service.
3. In addition to the 7-day food diary and the diet /alcohol counseling during clinic visits, telephone calls from a dietitian or qualified study personnel to assess as to how each patient is maintaining their diet will be conducted randomly during the treatment and post treatment follow-up periods.

6.2.9 Family History

Family history of hypertriglyceridemia and pancreatitis will be collected for each patient.

6.2.10 Chart Review for Incidents of Acute Pancreatitis in Medical History (Group 2)

Patient records will be reviewed for incidents of acute pancreatitis occurring up to 5 years prior to screening and information relating to these events will be collected for independent adjudication.

6.3 Restriction on the Lifestyle of Patients

6.3.1 Contraception Requirements

All male patients and women of childbearing potential must refrain from sperm/egg donation and either be abstinent or, if engaged in sexual relations of child-bearing potential, practice effective contraception from the time of signing the informed consent form until at least 13 weeks after their last dose of study treatment.

Male patients must also encourage their female partner to use effective contraception from the time of signing the informed consent until 13 weeks after the subject's last dose of study treatment.

For the purposes of this Study, women of childbearing potential are defined as any female who has experienced menarche, and who does not meet 1 of the following conditions:

- Postmenopausal: 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved
- 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Post hysterectomy

For the purposes of the study, effective contraception is defined as follows:

For male patients:

- Effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the use of condoms together with spermicidal foam/gel/film/ cream/suppository. Male patients must also encourage their female partner to use effective contraception from the time of signing the informed consent until 3 months after the patient's last dose of study treatment. Effective contraceptive for the female partner includes: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or barrier methods (female condom*, diaphragm, sponge, cervical cap) together with spermicidal foam/gel/film/cream/suppository. Male patients with partners that are pregnant must use condoms to ensure that the fetus is not exposed to the Study Drug.

For female patients:

- Using 1 or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or any 2 barrier methods (a combination of male or female condom* with diaphragm, sponge, or cervical cap) together with spermicidal foam/gel/film/cream/suppository.

* Note: A female condom and a male condom should not be used together as friction between the two can result in either product failing.

† Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception

6.3.2 Other Requirements

All patients will be required to fast for at least 10 hours and preferably not more than 12 hours before visits requiring fasted blood sampling.

All patients will be encouraged to follow a diet comprising ≤ 20 g fat per day during the study.

Alcohol should not be consumed during the study.

All patients will be given an instruction card that must be presented to the treating physician if a suspected case of pancreatitis occurs. The card will explain that the patient is in a clinical trial and that serum lipase and/or amylase measures should be done in order to adjudicate the event, based on Atlanta Classification (Banks et al. 2013). If serum or amylase activity is less than 3 x upper limit of normal (ULN), imaging, preferably contrast-enhanced computed tomography, should be considered to confirm the diagnosis of acute pancreatitis per the Atlanta Criteria.

7. STUDY DRUG

7.1 Volanesorsen Description

Volanesorsen drug product (ISIS 304801) characteristics are listed in Table 1.

Volanesorsen (ISIS 304801) is contained in glass prefilled syringes (PFS). Volanesorsen and its storage and preparation instructions will be provided by the Sponsor or designee. Volanesorsen must be stored securely at 2 °C to 8 °C and be protected from light.

Table 1 Volanesorsen (ISIS 304801) Characteristics

Strength	200 mg/mL
Volume/Formulation	1.5 mL solution per PFS
Dose	300 mg once weekly
Route of Administration	SC

7.2 Packaging and Labeling

The Sponsor will provide the Investigator with packaged volanesorsen labeled (ISIS 304801) in accordance with specific country regulatory requirements.

7.3 Study Drug Accountability

The study staff is required to document the receipt, dispensing, and return/destruction of volanesorsen provided by the Sponsor. The Study Center must return all unused volanesorsen to the Sponsor or designee. All used syringes must be disposed of as per the site's hazardous waste destruction policy.

8. TREATMENT OF PATIENTS

8.1 Volanesorsen Administration

For each individual patient, volanesorsen will be administered subcutaneously as a single 1.5 mL 300 mg injection once weekly for Weeks 1-52. Patients entering this ISIS 304801-CS7 study on a reduced dose or dose frequency of Study Drug (volanesorsen), for safety or tolerability reasons in their index study (ISIS 304801-CS6 or ISIS 304801-CS16), will continue to receive Study Drug as a single 300 mg/1.5 mL injection once-weekly for Weeks 53-156 as outlined in Sections 8.5 and 8.6. Patients on dose reduction will receive 300 mg/1.5 mL injections every 2 weeks.

Patients should receive 1 dose per week, unless on a dose reduction of 300 mg every 2 weeks, with weeks always defined relative to Study Day 1. For example, if a patient receives the first dose on a Monday, subsequent doses should be given on Mondays, if possible. If a patient misses an injection, or if treatment

on the usual day is not possible, the patient can reschedule the injection provided that 2 doses are administered at least 2 days apart.

Please refer to the Study Drug Manual provided by the Sponsor for more detailed instructions for volanesorsen preparation and administration.

8.2 Other Protocol-Required Drugs

There are no other protocol-required drugs.

8.3 Other Protocol-Required Treatment Procedures

There are no other protocol required treatment procedures for this study.

8.4 Treatment Precautions

There are no specific treatment precautions required for this study.

8.5 Safety Monitoring Rules

Please refer also to the 'Guidance for Investigator' section of the Investigator's Brochure.

For the purposes of safety monitoring baseline is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 (e.g., qualification assessments or assessments from the final visits of ISIS 304801-CS6 and ISIS 304801-CS16 index studies if used for qualification).

In addition to the standard monitoring of clinical safety parameters, the following guidelines are provided for the monitoring of selected parameters chosen based on preclinical and clinical observations.

Confirmation Guidance: At any time during the study (Treatment or Post-Treatment Periods), the initial clinical laboratory results meeting the safety monitoring or stopping criteria presented below **must be confirmed** by performing measurements (ideally in the same laboratory that performed the initial measurement) on new specimens. All new specimen collections should take place as soon as possible (ideally within 3 days of the initial collection). For stopping rules, if the initial laboratory result is observed during the Treatment Period, the results from the retest **must be available** prior to administering the next dose of volanesorsen.

In addition to the safety monitoring parameters listed below, the Sponsor may request confirmation of additional lab values.

Re-treatment Guidance: Patients with initial laboratory test values that reach a stopping rule must not be re-dosed until the re-test results are available. In general, patients who do not meet the stopping rules based upon retest may continue treatment. However, the Investigator and the Sponsor Medical Monitor (or appropriately qualified designee) should confer as to whether additional close monitoring of the patient is appropriate. Reduction in dose or dose frequency may also be initiated as noted in Section 8.7. If any of the stopping criteria described below (refer to Sections 8.6.1 to 8.6.3) are met, the patient will be dose paused or permanently discontinued (as described in the stopping criterion concerned) from further treatment with volanesorsen and evaluated fully as outlined below and in consultation with the Sponsor Medical Monitor or appropriately qualified designee and will be followed up in accordance with Section 8.8 of the protocol.

8.5.1 Safety Monitoring for Liver Chemistry Tests

The following rules are adapted from the draft guidance for industry, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," issued by the U.S. Department of Health and Human Services, Food and Drug Administration, July 2009. For a definition of Baseline please refer to guidance in Section 8.5 above.

In the event of an ALT or AST measurement that is > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) at any time during the study (Treatment or Post-Treatment Period), the initial measurement(s) should be confirmed as described above. Additional confirmatory measurements should also be performed if ALT or AST levels increase to 5 x ULN.

Frequency of Repeat Measurements: Patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) should have their liver chemistry tests (ALT, AST, alkaline phosphatase (ALP), international normalized ratio (INR) and total bilirubin) retested at least once-weekly until ALT and AST levels become ≤ 1.2 x ULN or 1.2 x baseline value if the baseline value was > ULN.

Further Investigation into Liver Chemistry Elevations: For patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), the following evaluations should be performed:

1. Obtain a more detailed history of symptoms and prior and concurrent diseases
2. Obtain further history for concomitant drug use (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
3. Obtain a history for exposure to environmental chemical agents and travel
4. Serology for viral hepatitis (HAV IgM, HBsAg, HCV antibody, CMV IgM, and EBV antibody panel)
5. Serology for autoimmune hepatitis (e.g., antinuclear antibody [ANA])

Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic CT or MRI scans, may be performed at the discretion of the Investigator, in consultation with the Sponsor Medical Monitor. Repetition of the above evaluations should be considered if a patient's ALT and/or AST levels reach 5 x ULN.

8.5.2 Safety Monitoring for Platelet Count Results

Actions to be taken in the event of reduced platelet count are shown in Table 3 in Section 8.6.3.

Monitor every 1 week unless otherwise specified. In addition, platelet function may be evaluated at any time during the study by aggregometry, using an approved point-of-care diagnostic device, in some patients. This additional functional testing may be performed at selected study centers.

Study Drug administration is contingent on the availability of the immediately preceding test result. An interpretable platelet value must be available within 7 days prior to treatment. Only the study doctor or qualified designee can authorize continued Study Drug administration based on an acceptable platelet value. Patients should not administer a dose until they have been contacted by their study doctor or designee and told that it is acceptable to dose. Authorization to dose must be documented in the patient's medical records.

Due to the 1 to 3-year study duration it is anticipated that patients may undertake travel including vacations, which may impede weekly platelet monitoring. In some situations, it may be possible to arrange for local laboratory testing or use of the home healthcare service at their temporary location. The intent is to maintain weekly platelet monitoring and treatment where possible, as well as Investigator site contact with the study patients. However, if the above options are not possible, a temporary interruption of study treatment will be planned with a platelet count drawn within 3-5 days prior to departure and with a prompt blood draw upon the patient's return which must be reported and reviewed by the Investigator prior to the patient resuming treatment.

Patients on dose pause should be monitored as per the platelet monitoring rules outlined in Section 8.8.1 until Study Drug administration is resumed.

The tests outlined in Table 2 should also be performed as soon as possible. Additional lab tests will be determined by the Sponsor Medical Monitor or designee in consultation with the Investigator.

Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor (See also Stopping Rules Section 8.6.3).

Table 2 Labs to Be Performed in the Event of a Platelet Count Less than the Lower Limit of Normal (×2) or < 100,000/mm^3 (×1)*

*In patients who have any 2 occurrences (consecutive or non-consecutive) of platelet count less than the lower limit of normal or who have any 1 occurrence of platelets < 100,000/mm^3. Labs only need to be performed once. Labs may be collected over multiple visits, if blood requirements are a concern, as per investigator discretion.

Note: The following labs may change as additional data is assessed, and sites will be updated regarding any changes.

To Be Performed at Local Lab
Peripheral smear (should be performed locally, fixed and sent to central lab for review)
Fibrinogen split products or D-dimer on fresh blood
To Be Performed at Central Lab
Citrated sample for platelets
Coagulation panel (PT/INR, aPTT)
CBC with reticulocytes
Folate (folic acid)
Vitamin B12
Fibrinogen
von Willebrand factor
Total globulins, total IgA, IgG and IgM
Complement: total C3, total C4, Bb, C5a
hsCRP
Helicobacter pylori (breath test)
Serology for:
HBV, HCV, HIV (if not done recently for screening)
Rubella
CMV
EBV
Parvo B19

Auto-antibody screen:
Antiphospholipid
Rheumatoid factor
Anti-dsDNA
Anti-thyroid
To Be Performed at Specialty Lab(s)
Antiplatelet antibodies and Anti-PF4 assay
Anti-ASO antibody

8.5.3 Safety Monitoring for Minor Bleeding Events

Minor bleeding events are those that do not fulfill the criteria for major bleeding or clinically-relevant, non-major bleeding events (which are defined in Section 8.6.3), for example excess bruising, petechiae, gingival bleeding on brushing teeth. If a minor bleeding event occurs, the Investigator must notify the Sponsor Medical Monitor and additional testing of coagulation parameters activated partial thromboplastin time (aPTT), prothrombin time (PT), INR and platelet count should be performed.

8.5.4 Safety Monitoring for Constitutional Symptoms

Patients will be instructed to promptly report any signs of symptoms of fever or constitutional symptoms that may arise during the study and the Investigator should closely evaluate all potential causes, including concomitant illness. Patients that experience persistent constitutional symptoms should be discussed with the Sponsor Medical Monitor or designee to determine whether additional monitoring or laboratory tests are required.

Should a patient experience constitutional or flu-like symptoms after Study Drug administration, investigators may consider additional laboratory assessments. For example, plasma and serum samples may be drawn for complement (Total C3, C4, C5a and Bb), hsCRP and for cytokine analysis.

8.5.5 Safety Monitoring for LDL-C Elevations

Beginning at Week 13, laboratory alerts will be in place to notify the Investigator if a patient has a low-density lipoprotein-cholesterol (LDL-C) > 160 mg/dL (> 130 mg/dL for patients with T2DM) on 2 consecutive visits. If this occurs, LDL-C values for this patient will be unblinded for the remainder of the study and the Investigator will be encouraged to initiate/adjust treatment to lower LDL-C according to country-specific guidelines (e.g., initiate statin therapy or increase the statin dose for patients who are already on treatment).

8.5.6 Safety Monitoring for Insulin, Oral Antidiabetic Medication and Glucose

All patients on insulin will monitor their glucose levels with a glucometer as per standard practice guidelines and bring their glucometer or glucometer log printout to every clinic visit. In addition, patients who are not on insulin but use a glucometer should also bring their glucometer and/or glucometer log printout to every clinic visit.

- The Investigator or delegate will review the glucometer reading or printout at every clinic visit to evaluate if fasting pre-breakfast self-monitored plasma glucose values exceed threshold values as per the Safety Monitoring Rules for Hyperglycemia below.

All diabetic patients will note any changes in their insulin dose and /or oral antidiabetic therapy, as well as any hypoglycemic episode they may experience.

- The Investigator or delegate will ask patients at every clinic visit if they made changes in their insulin dose or oral antidiabetic therapy, and if they experienced a hypoglycemic episode.
    - Patients will be instructed on the monitoring and management of hypoglycemic episodes at each visit.
    - Documented symptomatic hypoglycemic episodes should be captured as adverse events in the adverse event case report form (CRF). Documented symptomatic hypoglycemia is defined as typical hypoglycemia symptoms accompanied by measured plasma glucose ≤ 70 mg/dL (≤ 3.9 mmol/L).
    - Any changes in insulin dose or oral antidiabetic therapy should be captured into the Concomitant Medication CRF.

8.5.7 Safety Monitoring for Documented Severe Hypoglycemia

A **documented severe hypoglycemic event** is defined as one in which the patient requires assistance of another person to obtain treatment for the event and has a plasma glucose level ≤ 70 mg/dL (≤ 3.9 mmol/L). The rescue treatment of hypoglycemia may include IV glucose or buccal or intramuscular glucagon.

The definition of severe symptomatic hypoglycemia includes all episodes in which neurological impairment was severe enough to prevent self-treatment and which were thus thought to place patients at risk for injury to themselves or others. Note that "requires assistance" means that the patient could not help himself or herself. Someone being kind that assists spontaneously the patient when not necessary does not qualify as "requires assistance."

Severe hypoglycemia will be qualified as a SAE only if it fulfills SAE criteria.

If a patient presents with symptoms of hypoglycemia, the Investigator will need to take immediate action to confirm the patient's glucose level and treat the patient accordingly.

The experience of hypoglycemia may vary greatly from patient to patient. However, there are certain classical signs and symptoms, of which patients should be aware as a clue that their blood glucose may be low. Common symptoms include headache, heart pounding, confusion, disorientation, numbness or tingling, pale skin, shakiness or tremulousness, increased appetite, anxiousness or nervousness, lightheadedness or dizziness, sweating, and weakness. Coma could occur if blood sugar correction is not performed.

If patients suspect they might be having a hypoglycemia reaction, they should check their blood glucose using their meters as soon as possible, before treatment if possible, provided they feel it is safe to do so. If there is doubt about safety they should treat the event first, using some sugar, milk, or juice for example, then obtain and record a blood glucose value as soon as possible thereafter. The time and nature of treatment should be noted, and especially if any blood glucose result was before or after treatment. It would be helpful for the patient to note if a contributory factor (e.g., missed or reduced meals, unaccustomed physical activity) occurred earlier in the day of the event.

8.5.8 Safety Monitoring for Hyperglycemia

Upward dose titration and/or addition of any other anti-hyperglycemic agent(s) will not be allowed during the course of the study, unless specific threshold values are met at Week 13 or later and confirmed on subsequent testing (ideally within 1 week of the initial test).

HbA1c is monitored every 3 months throughout the study. In addition, patients on insulin should self-monitor their plasma glucose (SMPG) routinely on a glucometer as per practice guidelines. If a fasting pre-breakfast SMPG value exceeds the specific glycemic limit, the patient should check it again on the following 2 days. If all the fasting pre-breakfast values on 3 consecutive days exceed the specific limit, the patient should contact the Investigator and an unscheduled central laboratory fasting plasma glucose (FPG) measurement and HbA1c should be performed.

The threshold values are defined as:

- FPG > 270 mg/dL (15.0 mmol/L)
- HbA1c > 9% (for patients with baseline HbA1c < 8% and HbA1c increase of more than 1% from baseline (for patients with baseline HbA1c ≥ 8 and < 9%)

In case of confirmed FPG/HbA1c above the threshold value, the Investigator should ensure that no reasonable explanation exists for insufficient glucose control and in particular that:

- Plasma glucose was actually measured in the fasting condition (i.e., after at least 10 hours fast)
- Absence of intercurrent disease which may jeopardize glycemic control. In case of an emergency (e.g., surgery, infection), the Investigator can take appropriate measures for glycemic control
- Compliance to treatment is appropriate
- Compliance to diet and lifestyle is appropriate

If any of the above can reasonably explain the insufficient glycemic control, the Investigator should consider the following:

- Investigation and treatment of intercurrent disease (to be reported in adverse event (AE)/concomitant medication parts of the e-CRF)
- Stress on the absolute need to be compliant to treatment
- Organize a specific interview with a Registered Dietician or other qualified nutrition professional and stress on the absolute need to be compliant to diet and lifestyle recommendations

A FPG/HbA1c follow-up assessment should be arranged after appropriate action has been taken. If none from the above-mentioned reasons can be found, or if appropriate action fails to decrease FPG/HbA1c under the threshold values, additional medication may be introduced at the Investigator's discretion and according to local guidelines after discussion with the Sponsor Medical Monitor.

8.5.9 Acute Pancreatitis

If a patient has an episode of acute pancreatitis, treatment with Study Drug should be suspended temporarily until the patient is clinically stable. The suitability of the patient for continued treatment and the need for any modification to treatment schedule (refer to Section 8.7) will be determined by the Investigator in consultation with the Study Medical Monitor.

8.6 Stopping Rules

For the purposes of stopping rules baseline is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1.

8.6.1 Stopping Rules for Liver Chemistry Elevations

In the event of laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor,** treatment of a patient with volanesorsen will be stopped permanently; values that are not confirmed due to failure to retest or missing lab values will be presumed confirmed:

1. ALT or AST > 8 x ULN, which is confirmed
2. ALT or AST > 5 x ULN, which is confirmed and persists for ≥ 2 weeks
3. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed **and** total bilirubin > 2 x ULN or INR > 1.5
4. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed, and the new appearance (i.e., onset coincides with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> ULN) felt by the Investigator to be potentially related to hepatic inflammation

8.6.2 Stopping Rules for Renal Function Test Results

In the event of a persistent elevation that is observed over 2 consecutive weeks, for any of the 3 criteria below, treatment of a patient with volanesorsen may be stopped temporarily:

1. Serum creatinine increase that fulfill all of the following criteria: ≥ 0.3 mg/dL (26.5 µmol/L) and ≥ 40% above baseline creatinine values and > ULN
2. Proteinuria, dipstick 2 + (confirmed by dipstick retest and then further confirmed by a quantitative total urine protein measurement of > 1.0 g/24 hour)
3. Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault ≤ 40 mL/min that is confirmed by a 24-hour urine collection

The possible treatment re-initiation or follow-up schedule for any events meeting either of these criteria will be determined by the Investigator **in consultation with** the Sponsor Medical Monitor or designee.

8.6.3 Stopping Rules for Platelet Count Results

Actions to be taken in the event of a low platelet count are summarized in Table 3 below.

In the event of a platelet count less than 75,000/mm^3 that is associated with major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), treatment of a patient with volanesorsen will be stopped permanently. The follow-up schedule for any events meeting this stopping criterion will be determined by the Investigator in consultation with the Sponsor Medical Monitor.

In the event of any platelet count less than 50,000/mm^3, or a rate of decline ≥ 50% between two consecutive assessments, irrespective of the platelet level, or a platelet count less than 75,000/mm^3 that

occurs while the patient is on treatment at 300 mg every 2 weeks, then treatment of a patient with volanesorsen will be stopped permanently. Platelet count will be monitored as outlined in Table 3.

Administration of steroids is recommended for patients whose platelet count is less than 50,000/mm^3. Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (**note:** may require continuation with oral steroids after methylprednisolone). In order to reduce the unlikely but potential increased risk of pancreatitis during the period of corticosteroid therapy, triglyceride levels will be monitored weekly, and AE monitoring will continue, during corticosteroid treatment and the laboratory alert will be changed from an increase of 2,000 to 500 mg/dL during that period.

In the event of a platelet count less than 75,000/mm^3, and in the absence of major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), treatment of a patient with volanesorsen should be suspended temporarily until the platelet count has recovered to> 100,000/mm^3. If treatment is continued it should be at a reduced dose frequency of 300 mg every 2 weeks (refer to Section 8.7). The suitability of the patient for continued treatment will be determined by the Investigator in consultation with the Study Medical Monitor and will be based on factors such as the original rate of decline in the patient's platelet count, whether any bleeding events were experienced by the patient, and the speed of recovery of platelet count upon holding of treatment.

If after the first treatment rechallenge the platelet count again falls below 75,000/mm^3, then treatment of the patient with Study Drug will be stopped permanently.

Definition of Major Bleeding Events (Schulman et al. 2005):

- Fatal bleeding, and/or
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarterial or pericardial, or intramuscular with compartment syndrome, and/or
- Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more within 24 hours, or leading to transfusion of 2 or more units of whole or red cells

Definition of Clinically-Relevant, Non-Major Bleeding Events (Schulman et al. 2005):

1. Multiple-source bleeding
2. Spontaneous hematoma > 25 cm^2
3. Excessive wound hematoma (not injection site related)
4. Macroscopic hematuria (spontaneous or lasting > 24 hours if associated with an intervention)
5. Spontaneous rectal bleeding; epitasis, gingival bleeding, hemoptysis, hematemesis
6. Bleeding after venipuncture for > 5 minutes

Table 3 Actions in Patients with Low Platelet Count

Platelet Count on Rx	Drug Dose	Monitoring
	Study Drug administration is contingent on the availability of the immediately preceding test result. An interpretable platelet value must be available within 7 days prior to treatment. Only the study doctor or qualified designee can authorize continued Study Drug administration based on an acceptable platelet value. Patients should not administer a dose until they have been contacted by their study doctor or designee and told that it is acceptable to dose. Authorization to dose must be documented in the patient's medical records.	Monitor every 1 week unless otherwise specified In addition, platelet function may be evaluated during the study by aggregometry, using an approved point- of-care diagnostic device, in some patients. This additional functional testing may be performed at selected study centers. Patients on dose pause should be monitored as per the platelet monitoring rules outlined in Section 8.8.1 until Study Drug administration is resumed. Obtain additional lab tests (Table 2) if 2 occurrences consecutive or non-consecutive of platelet count 140K - > 100K/mm^3 or 1 occurrence of platelet count ≤ 100K/mm^3. Labs only need to be performed once. Labs may be collected over multiple visits, if blood requirements are a concern, as per Investigator discretion.
> 100K/mm^3	Once weekly 300 mg Study Drug administration	
100K/mm^3 - >75K/mm^3	Permanently reduce dose frequency to 300 mg every 2 weeks.	
75K/mm^3 - >50K/mm^3	• If occurs while on dose of 300 mg every 2 weeks, then permanently discontinue Study Drug, otherwise dose pause. If dose pause is ≥ 3 months then patient must discontinue treatment and enter the follow up period. • When platelet count returns to > 100K/mm^3 restart treatment at dose frequency of 300 mg every 2 weeks in consultation with the Sponsor Medical Monitor	• Monitor every 2-3 days until 2 successive values are > 75K/mm^3 then monitor every 1 week • Consider discontinuation of antiplatelet agents/NSAIDS/ anticoagulant medication
< 50K/mm^3 or a rate of decline ≥ 50% between two consecutive assessments, irrespective of the platelet level	Permanently discontinue Study Drug and the patient will enter the follow up period.	• Monitor daily until 2 successive values show improvement then monitor every 2-3 days until 2 successive values are > 75K/mm^3 then monitor every 1 week • Patient should be evaluated by a hematologist to provide diagnostic and therapeutic management • Steroids recommended *. It is strongly recommended that, unless

Platelet Count on Rx	Drug Dose	Monitoring
		the patient has a medical contraindication to receiving glucocorticoids, the patient receives glucocorticoid therapy to reverse the platelet decline. • Monitor triglyceride levels weekly and continue AE monitoring during steroid therapy • Discontinue antiplatelet agents/ NSAIDS/ anticoagulant medication while platelet count is< 50K/mm^3 if possible.

Legend:

* Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (**note**: may require continuation with oral steroids after Methylprednisolone). In order to reduce the unlikely but potential increased risk of pancreatitis during the period of corticosteroid therapy, triglyceride levels will be monitored weekly, and AE monitoring will continue, during corticosteroid treatment and the laboratory alert will be changed from an increase of 2,000 to 500 mg/dL during that period.

8.7 Adjustment of Dose Frequency

Dose adjustments for platelet count reduction must be made in accordance with Section 8.6.3 and Table 3 (above).

Other dose adjustments, including dose interruptions, and/or decreasing the dose frequency to 300 mg every 2 weeks will be allowed for safety and tolerability. Any proposed adjustment to treatment schedule must be discussed with, and approved by, the Study Medical Monitor prior to initiation. Up to 2 adjustments in the treatment schedule may be allowed.

Patients may be dose paused in response to AEs, and the Study Medical Monitor is informed. If a patient is dose paused for ≥ 3 months, he or she is considered to have discontinued treatment and should enter the 26-week post-treatment follow-up period.

8.8 Discontinuation of Study Treatment

A patient must permanently discontinue study treatment for any of the following:

- The patient becomes pregnant. Report the pregnancy according to instructions in Section 9.5.4
- The patient withdraws consent
- The patient experiences an AE that necessitates permanent discontinuation of study treatment
- The patient develops laboratory test abnormalities that meet any of the stopping rules listed in Section 8.6
- The patient is dose paused for ≥ 3 months

The reason for discontinuation of study treatment must be recorded in the CRF and source documentation.

8.8.1 Follow-up Visits for Early Termination from Treatment Period

Any patient who discontinues early from the Treatment Period should be followed as per the platelet monitoring rules shown in Table 3 in Section 8.6.3 for the first 6 weeks after discontinuing Study Drug. Following this period, if the platelet count is stable (at least 3 consecutive values that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3), the next platelet count should be taken within at least 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug. Any patient who discontinues treatment after Week 44 should also be strongly encouraged to attend a final follow-up visit (Week 78 visit assessments) approximately 26 weeks after their last dose of Study Drug.

A patient who discontinues early from treatment with stable platelet counts above the LLN at the time of treatment discontinuation will have platelet counts drawn every 2 weeks after discontinuing Study Drug for the first 6 weeks after the last dose of Study Drug. A subsequent platelet count should then be taken after an additional 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug.

If the patient declines or is unable to participate in the above, an early termination (ET) visit (Week 52 visit assessments) should be performed at the time of withdrawal, at a minimum, and ideally within 2 weeks from the last dose of Study Drug.

8.8.2 Follow-up Visits for Early Termination from Post-Treatment Follow-up Period

The patient who requests to withdraw from the study during the Post-Treatment Follow-up Period should be encouraged to follow the platelet monitoring rules shown in Table 3 in Section 8.6.3 for the first 6 weeks after discontinuing Study Drug. Following this period, if the platelet count is stable (at least 3 consecutive values that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3), the next platelet count should be taken within at least 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug. Patients should also be encouraged to undergo a final follow-up visit (Week 78, see Appendix A) prior to leaving the study.

If a patient withdraws due to an AE at any time during the study, the Investigator should arrange for the patient to have appropriate follow-up until the AE has resolved or stabilized.

8.9 Withdrawal of Patients from the Study

Patients must be withdrawn from the study for any of the following:

- Withdrawal of consent
- The patient is unwilling or unable to comply with the protocol

Other reasons for withdrawal of patients from the study might include:

- At the discretion of the Investigator for medical reasons
- At the discretion of the Investigator or Sponsor for noncompliance
- Significant protocol deviation
- Commercialization of product

All efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information, including the reason for withdrawal from study, must be recorded in the CRF.

Any patient who withdraws consent to participate in the study will be removed from further treatment and study observation immediately upon the date of request. These patients should be encouraged to complete the ET study procedures and observations at the time of withdrawal (see Section 8.8 and Appendix A).

For patients withdrawn for reasons other than withdrawal of consent every effort should be made to complete the early termination study procedures and observations at the time of withdrawal (see Section 8.8 and Appendix A).

8.10 Concomitant Therapy and Procedures

The use of concomitant therapies or procedures defined below must be recorded on the patient's CRF. AEs related to administration of these therapies or procedures must also be documented on the appropriate CRF.

8.10.1 Concomitant Therapy

A concomitant therapy is any non-protocol specified drug or substance (including over-the-counter medications, herbal medications and vitamin supplements) administered between signing informed consent and completion of the post-treatment follow-up period. All concomitant medications/treatments and significant non-drug therapies (including supplements and assistive devices) received by a patient, including changes in the patient's current medications, must be recorded in the patient's source documents and CRF. Patients taking over the counter (OTC) omega-3 fatty acids should make every effort to remain on the same brand throughout the study.

Allowed Concomitant Therapy

Any medications deemed necessary by the Investigator are allowed except those listed in the disallowed concomitant therapy.

Disallowed Concomitant Therapy

No lipid lowering therapies (e.g., fibrates, niacin, fish oil or other products containing omega-3 fatty acids [including OTC preparations]), GLP-1 agonists, Glybera, or systemic corticosteroids may be started or adjusted after baseline Qualification. Doses of existing oral anti-diabetic medication, oral contraceptives, hormone replacement therapy, anticoagulants, or drugs or dietary supplements with potential lipid-altering effects should not be adjusted. Study patients are prohibited from receiving other experimental agents during the study. This includes marketed agents at experimental dosages that are being tested for the treatment of hypertriglyceridemia.

Patients should consult with the Site Investigator or designee prior to initiating any new medication, including non-prescription or herbal compounds or any other non-drug therapy.

8.10.2 Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between signing of

informed consent and Week 78 (or Week 130 or 182 if the patient enters the first or second extended treatment period, respectively) visit.

Disallowed Concomitant Procedure

Plasma apheresis is not allowed during the study.

8.11 Treatment Compliance

Compliance with treatment is to be monitored and recorded by Study Center staff. The Study Center staff is required to document the receipt, dispensing, and return/destruction of volanesorsen. Patients that are self-administering volanesorsen at home must record treatment in a treatment diary that will be reviewed periodically by Study Center staff and the Clinical Monitor.

9. SERIOUS AND NON-SERIOUS ADVERSE EVENT REPORTING

9.1 Sponsor Review of Safety Information

Safety information will be collected, reviewed, and evaluated by the Sponsor in accordance with the Safety Management Plan throughout the conduct of the clinical trial.

9.2 Regulatory Requirements

The Sponsor is responsible for regulatory submissions and reporting to the Investigators of serious adverse events (SAEs) including suspected unexpected serious adverse reactions (SUSARs) per the International Conference on Harmonization (ICH) guidelines E2A and ICH E6 (R2). Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines.

Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) will be notified of any SAE according to applicable regulations. The Independent DSMB will be notified of any SAE as specified in the DSMB charter.

In addition to the Investigator's assessment of relatedness, the Sponsor or designee will evaluate the available information and perform an independent assessment of relatedness. While the Sponsor may upgrade an Investigator's decision it is not permissible to downgrade the Investigator's opinion for the purposes of determining whether the SAE meets the definition of a SUSAR.

The following table identifies the SAEs that the Sponsor or designee will not report on an individual basis in an expedited manner because they are anticipated to occur in the study population independent of volanesorsen exposure. The Investigator still has the responsibility to report all SAEs to the Sponsor as described in Sections 9.4.1 to 9.4.3.5.

Table 4 Expected Event for the Protocol Defined Population by Preferred Term and the Expected Incidence

Preferred Term	Expected Incidence in the Protocol Defined Population (Gaudet et al. 2010 and 2013)
Pancreatitis associated events including the PTs of hereditary pancreatitis, pancreatitis, pancreatitis acute, pancreatitis chronic, pancreatitis necrotizing, pancreatitis relapsing	0.2-0.35 events per patient-year

Fatal pancreatitis associated events will be considered as unexpected and are reportable. The Sponsor and DSMB will monitor non-fatal pancreatitis associated SAEs using the incidence rate of the event compared to the rate expected in a non-volanesorsen exposed population. If the aggregate analysis indicates that an event is occurring significantly more frequently or at a greater severity than expected, then the event will be reported.

SAEs not specified in the table will be evaluated on case by case basis to determine whether there is a reasonable possibility that the drug caused the event. If the event is considered by the Sponsor or designee to meet the definition of a SUSAR the event will be reported.

9.3 Definitions

9.3.1 Adverse Event

An adverse event is any unfavorable and unintended sign (including a clinically-significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the study or use of investigational drug product, whether or not the AE is considered related to the investigational drug product.

9.3.2 Adverse Reaction and Suspected Adverse Reaction

An adverse reaction is any adverse event caused by volanesorsen.

A suspected adverse reaction is any adverse event for which there is a reasonable possibility that volanesorsen drug caused the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

9.3.3 Serious Adverse Event (SAE)

A serious adverse event is any adverse event that in the view of either the Investigator or Sponsor, meets any of the following criteria:

- Results in death
- Is life threatening: that is, poses an immediate risk of death at the time of the event

An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Hospitalization is defined as an admission of greater than 24 hours to a medical facility and does not always qualify as an AE
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly or birth defect in the offspring of the patient (whether the patient is male or female)
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered serious when, based upon appropriate medical judgment,

they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

9.4 Monitoring and Recording Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the study (i.e., before informed consent) should be recorded as Medical History and not recorded as AEs unless the pre-existing condition worsened. The Investigator should always group signs and symptoms into a single term that constitutes a **single unifying diagnosis** if possible.

9.4.1 Serious Adverse Events

In the interest of patient safety, and in order to fulfill regulatory requirements**,** all SAEs (regardless of their relationship to volanesorsen) should be reported to the Sponsor or designee within 24 hours of the Study Center's first knowledge of the event. The collection of SAEs will begin after the patient signs the informed consent form and stop at the end of the patient's follow-up period which is defined as the Week 78 (or Week 130 or 182 if the patient enters the first or second extended treatment period, respectively) visit. When the Investigator is reporting by telephone, it is important to speak to someone in person versus leaving a message. An Initial Serious Adverse Event Form should be completed and a copy should be faxed to the Sponsor or designee.

Detailed information should be actively sought and included on Follow-Up Serious Adverse Event Forms as soon as additional information becomes available. All SAEs will be followed until resolution. SAEs that remain ongoing past the patient's last protocol-specified follow-up visit will be evaluated by the Investigator and Sponsor. If the Investigator and Sponsor agree the patient's condition is unlikely to resolve, the Investigator and Sponsor will determine the follow-up requirement.

9.4.2 Non-Serious Adverse Events

The recording of non-serious AEs will begin after the patient signs the informed consent form and will stop at the end of the patient's follow-up period, which is defined as the Week 78 (or Week 130 or 182 if the patient enters the first or second extended treatment period, respectively) visit. The Investigator will monitor each patient closely and record all observed or volunteered AEs on the Adverse Event Case Report Form.

9.4.3 Evaluation of Adverse Events (Serious and Non-Serious)

The Investigator's opinion of the following should be documented on the Adverse Event Case Report Form:

9.4.3.1 Relationship to the Study Drug

The event's relationship to volanesorsen is characterized by 1 of the following:

- **Related:** There is clear evidence that the event is related to the use of volanesorsen, e.g., confirmation by positive rechallenge test

- **Possible:** The event cannot be explained by the patient's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and volanesorsen administration
- **Unlikely/Remote:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to volanesorsen administration and/or exposure suggests that a causal relationship is unlikely (For reporting purposes, Unlikely/Remote will be grouped together with Not Related)
- **Not Related:** The event can be readily explained by the patient's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and volanesorsen

9.4.3.2 Severity

The severity of AEs and SAEs will be graded based on criteria from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010 (refer to Appendix D). Any AE not listed in Appendix D will be graded as follows:

- **Mild:** The event is easily tolerated by the patient and does not affect the patient's usual daily activities
- **Moderate:** The event causes the patient more discomfort and interrupts the patient's usual daily activities
- **Severe:** The event is incapacitating and causes considerable interference with the patient's usual daily activities

If the event is an SAE, then all applicable seriousness criteria must be indicated (criteria listed in Section 9.3.3).

9.4.3.3 Action Taken with Volanesorsen

Action taken with volanesorsen due to the event is characterized by 1 of the following:

- **None:** No changes were made to volanesorsen administration and dose
- **Permanently Discontinued:** Volanesorsen was discontinued and not restarted
- **Temporarily Interrupted, restarted – same dose:** Treatment was temporarily interrupted or delayed due to the AE and restarted at the same dose
- **Reduced schedule:** Treatment frequency was reduced

9.4.3.4 Treatment Given for Adverse Event

Any treatment (e.g., medications or procedures) given for the AE should be recorded on the Adverse Event Case Report Form (treatment should also be recorded on the concomitant treatment or ancillary procedures CRF as appropriate).

9.4.3.5 Outcome of the Adverse Event

If the event is a non-serious AE then the event's outcome is characterized by 1 of the following:

- **AE Persists:** Patient terminates from the trial and the AE continues

- **Recovered:** Patient recovered completely from the AE
- **Became Serious:** The event became serious (the date that the event became serious should be recorded as the Resolution Date of that AE and the Onset Date of the corresponding SAE)
- **Change in Severity** (if applicable): AE severity changed

If the event is a SAE then the event's outcome is characterized by 1 of the following:

- **Ongoing:** SAE continuing
- **Persists (as non-serious AE):** Patient has not fully recovered but the event no longer meets serious criteria and should be captured as an AE on the non-serious AE electronic Case Report Form (eCRF) (the SAE resolution date should be entered as the date of onset of that AE)
- **Recovered:** Patient recovered completely from the SAE (the date of recovery should be entered as the SAE resolution date)
- **Fatal:** Patient died (the date of death should be entered as the SAE resolution date)

9.4.4 Adjudication Committees

All SAEs that occur during the study that are consistent with a major acute cardiovascular event (MACE) will be adjudicated by a blinded, independent committee as outlined in the MACE Adjudication Charter.

All AEs and SAEs that occur during the study that are consistent with an event of acute pancreatitis will be adjudicated by a blinded, independent committee according to the Atlanta classification of acute pancreatitis (Banks et al. 2013) and as outlined in the Pancreatitis Adjudication Charter. In addition, data for prior episodes of acute pancreatitis or suspected pancreatitis will be collected by review of each patient's medical chart and these events will also be adjudicated.

9.5 Procedures for Handling Special Situations

9.5.1 Abnormalities of Laboratory Tests

Clinically-significant abnormal laboratory test results may, in the opinion of the Investigator, constitute or be associated with an AE. Examples of these include abnormal laboratory results that are associated with symptoms, or require treatment, e.g., bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac arrhythmias due to hyperkalemia. Whenever possible, the underlying diagnosis should be listed in preference to abnormal laboratory values as AEs. Clinically-significant abnormalities will be monitored by the Investigator until the parameter returns to its baseline value or until agreement is reached between the Investigator and Sponsor Medical Monitor. Laboratory abnormalities deemed not clinically-significant (NCS) by the Investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator should not be deemed NCS on the laboratory sheet.

The Investigator is responsible for reviewing and signing all laboratory reports. The signed clinical laboratory reports will serve as source documents and should include the Investigator's assessment of clinical significance of out of range/abnormal laboratory values.

9.5.2 Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the patient is hospitalized; the Study Center must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the patient's consent to participate in the study
- The condition that required the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the patient's consent to participate in the study and the timing of the procedure or treatment
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission

9.5.3 Treatment Errors

Volanesorsen treatment errors should be documented as Protocol Deviations. A brief description should be provided in the deviation, including whether the patient was symptomatic (list symptoms) or asymptomatic, and the event accidental or intentional.

Treatment details should be captured on the Treatment Case Report Form. If the patient takes a dose of volanesorsen that exceeds protocol specifications and the patient is symptomatic, then the symptom(s) should be documented as an AE and be reported per Section 9.4.

Should an overdose occur, the Investigator or designee should refer to the Guidance to Investigator's section of the Investigator's Brochure and contact the Sponsor or designee within 24 hours.

9.5.4 Contraception and Pregnancy

Male patients and female patients of childbearing potential must continue to use appropriate contraception with their partners, or refrain from sexual activity, as described in Section 6.3.1.

If a patient becomes pregnant or a pregnancy is suspected, or if a male patient makes or believes that he has made someone pregnant during the study, then the Study Center staff must be informed immediately. An Initial Pregnancy Form should be submitted to the Sponsor or designee **within 24 hours** of first learning of the occurrence of pregnancy. Follow-up information including delivery or termination is reported on Follow-up Pregnancy Forms and reported within 24 hours.

Payment for all aspects of obstetrical care, child or related care will be the patient's responsibility.

Female patients: If a suspected pregnancy occurs while on the study (including follow-up), a pregnancy test will be performed. The patient with a confirmed pregnancy will be immediately withdrawn from treatment with volanesorsen. However, the patient will be encouraged to complete the post-treatment follow-up portion of the study to the extent that study procedures do not interfere with the pregnancy. Regardless of continued study participation, the study physician will assist the patient in getting obstetrical care and the progress of the pregnancy will be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the Study Center and Sponsor may require access to the mother and infant's medical records for an additional 8 weeks after birth.

Male patients: The progress of the pregnancy in a male patient's partner should be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, **the Study Center and Sponsor may request access to the**

mother and infant's medical records for an additional 8 weeks after birth. Follow-up will be performed to the extent permitted by applicable regulations and privacy considerations.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints

For fasting lipid measurements, the values at Month 3 analysis time point are defined as the average of Week 12 (Day 78) and Week 13 (Day 85) fasting assessments, the values of Month 6 analysis time point is at the end of Month 6 are defined as the average of Week 25 (Day 169) and Week 26 (Day 176) fasting assessments, and the values at the Month 12 analysis time point are defined as the average of Week 50 (Day 344) and Week 52 (Day 358) fasting assessments.

10.1.1 Efficacy Endpoints

- Percent change and absolute change from baseline in fasting TG
- Frequency and severity of patient reported abdominal pain during the treatment period
- Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-HDL-C, apoB, HDL-C, apolipoprotein A-1 (apoA-1), VLDL-C, and LDL-C
- Percent change from baseline in fasting total apolipoprotein C-III
- Change in blood viscosity (may be evaluated)
- Quality of Life questionnaires (EQ-5D, SF-36)
- Adjudicated acute pancreatitis event rate
- Other symptoms: eruptive xanthoma, lipemia retinalis

10.1.2 Safety Endpoints

- Adverse events including adjudicated events of pancreatitis and MACE
- Vital signs and weight
- Physical examinations
- Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis)
- Echocardiography
- Electrocardiograms (ECGs)
- Use of concomitant medications
- MRIs
- Platelet aggregation (may be evaluated)

10.2 Sample Size

No sample size calculations were performed as this is an open-label study.

10.3 Populations

Full Analysis Set (FAS): All patients who are enrolled and received at least 1 dose of active Study Drug and have a baseline TG assessment. The FAS represents the practically-feasible intent-to-treat (ITT) population as delineated in ICH Guideline E9.

Per Protocol Set (PPS): Subset of the FAS who received 9 of first 13 scheduled doses of volanesorsen and with no significant protocol deviations that would be expected to affect efficacy and PD assessments. The detailed criteria will be specified and finalized prior to the final database lock.

Safety Set: All patients who are enrolled and receive at least 1 dose of volanesorsen.

PK Population: All patients who are enrolled, receive at least 1 dose of volanesorsen, and have at least 1 post first dose PK sample collected, analyzed, and reported.

10.4 Definition of Baseline

Definitions of baseline are given below for the purposes of the final analysis.

For fasting lipid measurements, 2 baselines are defined for each patient in Groups 1 and 2: Group 1 (ISIS 304801-CS6) or Group 2 (ISIS 304801-CS16) index study baseline and the baseline in this open-label study, which is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 (e.g., qualification assessments or assessments from final visit of the ISIS 304801-CS6 or ISIS 304801-CS16 index studies if used for qualification).

For other measurements, baseline for patients on active treatment in the ISIS 304801-CS6 or ISIS 304801-CS16 index study will be the ISIS 304801-CS6 or ISIS 304801-CS16 index study baseline. For patients on placebo in the ISIS 304801-CS6 or ISIS 304801-CS16 index study, baseline will be the last non-missing assessment prior to the first dose of Study Drug. Details will be provided in the SAP.

10.5 Interim Analysis

An interim analysis may be conducted after the last patient's Week 13 visit of the open-label study or after the database of the ISIS 304801-CS6 and ISIS 304801-CS16 index studies are locked and unblinded. Both safety and efficacy information from this open-label study may be summarized during this interim analysis. Efficacy analyses will be detailed in the SAP.

10.6 Planned Methods of Analysis

All eCRF data, lab data transfers, as well as any outcomes derived from the data, will be provided in the patient data listings. Patient data listings will be presented for all patients enrolled into the study. Descriptive summary statistics including n, mean, median, standard deviation, standard error, interquartile range (25th percentile, 75th percentile), and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data by treatment group of the index studies for patients on active Study Drug in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies, and pooled treatment naïve group which includes patients on placebo in index studies. Where appropriate, p-values will be reported. All statistical tests will be conducted using 2-sided tests with 5% Type I error rates unless otherwise stated.

TG related endpoints will be assessed in the FAS and PPS, and all other efficacy endpoints will be assessed in the FAS. All safety assessments will be performed on the Safety Set. PK endpoints will be assessed in the PK Set as applicable.

10.6.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics by treatment group and overall. The patient disposition will be summarized by treatment group and overall. All patients enrolled will be included in a summary of patient disposition.

10.6.2 Safety Analysis

Treatment duration and amount of Study Drug received will be summarized by treatment group and overall.

Patient incidence rates of AEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class, MedDRA preferred term, and treatment group of the index studies. Narratives of treatment-emergent deaths, serious and significant AEs, including early withdrawals due to AEs, will also be provided.

All treatment-emergent AEs, all treatment-emergent AEs potentially related to Study Drug, all treatment-emergent serious AEs, and all treatment-emergent serious AEs potentially related to Study Drug will be summarized.

Injection Site Reactions (ISRs) will be summarized by treatment group, MedDRA preferred term and severity.

Independently adjudicated events of MACE and pancreatitis will be summarized by treatment group.

Laboratory tests to ensure patient safety including chemistry panel, complete blood count (CBC) with differential, coagulation panel, IM, complement etc., will be summarized by study visits by treatment group.

These safety variables will also be presented as change and percent change from baseline over time after Study Drug administration, as appropriate.

Vital signs, weight, ECG measures, echocardiography assessments, and MRI assessments will be tabulated by treatment group.

10.6.3 Efficacy Analysis

Percent change and change from baseline to Month 3, Month 6, and Month 12 in fasting TG will be summarized by treatment group. Response rate of patients with fasting plasma TG < 750 mg/dL or achieving fasting TG ≥ 40% reduction from baseline at Month 3, Month 6, and Month 12 will be summarized. Response analysis will also be conducted using a range of fasting plasma TG thresholds for determination of responder status.

Percent change and change from baseline to Month 3, Month 6, and Month 12 will also be summarized by treatment group for other fasting lipid measures including non-HDL-C, apoB, HDL-C, apoA-1, VLDL-C, and LDL-C, total cholesterol, and fasting total apoC-III.

The incremental effects of volanesorsen on lipid measures will be explored and the association between changes in lipid parameters and total amount of drug received will be examined, as appropriate.

Frequency and severity of patient reported abdominal pain, adjudicated acute pancreatitis event rate, quality of life assessments, and comparison of other symptoms including eruptive xanthomas and lipemia retinalis will be summarized by treatment group.

Additional details of the analyses to be conducted will be provided in the SAP.

10.6.4 Pharmacokinetic and Immunogenicity Analysis

10.6.4.1 Pharmacokinetic Analysis

For all patients, pre-dose and post-treatment volanesorsen plasma concentrations will be summarized using descriptive statistics by treatment group and IM status.

For patients in the PK subgroup only, non-compartmental PK analysis of volanesorsen will be carried out on each individual patient data set using data collected in the open-label study from the intensive PK subgroup, following a single-dose (i.e., single-dose PK) or multiple doses (i.e., steady-state PK), depending on their earlier treatment in the index studies (Group 1 and 2 patients). On Week 1 Day 1 of the open-label study, patients who received placebo in the index study will receive the first treatment of volanesorsen (single-dose PK), while patients who received volanesorsen in the index studies had been on volanesorsen treatment for 12 months (ISIS 304801-CS6) or 6 months (ISIS 304801-CS16), thus the PK data collected from these patients reflect steady-state PK. The maximum observed drug concentration (C_{max}) and the time taken to reach C_{max} (T_{max}) will be obtained directly from the concentration-time data. Area under the plasma concentration-time curve from time zero to 24 hours (AUC_{0-24h}) will be calculated using the linear trapezoidal rule. Apparent systemic (plasma) clearance after SC administration (CL_{0-24h}/F) will be calculated from CL_{0-24h}/F = Actual Dose/AUC_{0-24h}. Mean residence time (MRT) from time zero to 24 hours after the SC administration will be calculated from the equation, $MRT_{0-24h} = AUMC_{0-24h} /AUC_{0-24h}$, where $AUMC_{0-24h}$ is the area under the moment plasma concentration-time curve from time zero to 24 hours after the SC administration. Other PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist.

Plasma PK parameters will be summarized using descriptive statistics by treatment group and IM status. Additional details regarding the PK analysis will be described in the SAP.

Population PK, PK/PD, and covariate analysis may be performed if deemed appropriate, and results will be reported separately.

10.6.4.2 Immunogenicity Analysis

Immunogenicity (IM) results (screen positive/negative, confirmed positive/negative or not evaluable, and when applicable, titer of anti-volanesorsen antibodies) before, during, and after treatment with Study Drug (volanesorsen) (i.e., sample [anti-drug antibody] ADA status) will be listed by their prior treatment in study ISIS 304801-CS6 or ISIS 304801-CS16 (Groups 1 and 2) and study day. Subject ADA status (positive/negative or not evaluable) for all evaluable patients, along with the study day associated with the first positive IM status emerged (T_{first}, i.e., onset of ADA development), the last positive IM status observed (T_{last}), the last ADA sample collection day, and subject - peak titer if applicable, will be listed by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16 (Groups 1 and 2) and study day. Subjects with positive anti-volanesorsen antibody status may be further classified (when applicable) as being either ‘persistent’, ‘transient’, or ‘not determinable’, if deemed appropriate.

Additionally, the sample and subject IM incidence (number) and incidence rate (percent) will be summarized as the total number and percent of evaluated subjects with antibody negative, positive, and unknown status by treatment group. Furthermore, onset and titer of the ADA response, if applicable, will be summarized as median, quartiles (25% and 75%), and range.

Additional details regarding the IM data analysis will be described in the SAP.

Potential relationships between immunogenicity results (e.g., IM status) and selected efficacy (e.g., % change in fasting TG from baseline at 3-, 6-, and 12-month endpoints), safety, and PK (e.g., C_{trough}) measures will be evaluated using graphical analysis and statistical analysis. These analyses will be either conducted and included in the study report, or data pooled and analyzed from all available Phase 2 and 3 studies and reported separately.

11. INVESTIGATOR'S REGULATORY OBLIGATIONS

11.1 Informed Consent

The written informed consent document should be prepared in the language(s) of the potential patient population, based on an English version provided by the Sponsor.

Before a patient's participation in the trial, the Investigator is responsible for obtaining written informed consent from the patient after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific qualification procedures or any Study Drug are administered. The patient must be given sufficient time to consider whether to participate in the study.

The acquisition of informed consent and the patient's agreement or refusal to notify his/her primary care physician should be documented in the patient's medical records and the informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion (not necessarily an Investigator). The original signed informed consent form should be retained in the Study Master File and in any other locations required by institutional policy, and a copy of the signed consent form should be provided to the patient.

11.2 Ethical Conduct of the Study

The Guidelines of the World Medical Association (WMA) Declaration of Helsinki dated October 2002 the applicable regulations and guidelines of current Good Clinical Practice (GCP) as well as the demands of national drug and data protection laws and other applicable regulatory requirements will be strictly followed.

11.3 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent form, other written patient information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by the Sponsor before recruitment of patients into the study and shipment of volanesorsen. A copy of the written approval of any other items/materials that must be approved by the Study Center or IEC/IRB must also be received by the Sponsor before recruitment of patients into the study and shipment of Study Drug. The Investigator's Brochure must be submitted to the IEC/IRB for acknowledgement.

The Investigator must submit to and, where necessary, obtain approval from the IEC/IRB, for all subsequent protocol amendments and changes to the informed consent document. The Investigator should notify the IEC/IRB of deviations from the protocol in accordance with ICH E6 (R2) Section 4.5.2. The Investigator should also notify the IEC/IRB of serious adverse events occurring at the Study Center and other adverse event reports received from the Sponsor, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study. Copies of the Investigator's reports, all IEC/IRB submissions and the IEC/IRB continuance of approval must be sent to the Sponsor.

11.4 Patient Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained. On the case report forms (CRF) or other documents submitted to the Sponsor, patients should be identified by unique initials and a patient study number only. Documents that are not for submission to the Sponsor (e.g., signed informed consent forms) should be kept in strict confidence by the Investigator.

In compliance with Federal and local regulations/ICH E6 (R2) Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the patient to permit named representatives to have access to his/her study-related records without violating the confidentiality of the patient.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments

Protocol amendments must be made only with the prior approval of the Sponsor. Agreement from the Investigator must be obtained for all protocol amendments and amendments to the informed consent document. The regulatory authority and IEC/IRB must be informed of all amendments and give approval for any amendments likely to affect the safety of the patients or the conduct of the trial. The Investigator **must** send a copy of the approval letter from the IEC/IRB to the Sponsor.

12.2 Study Termination

The Sponsor reserves the right to terminate the study according to the terms of the site contract. The Investigator reserves the right to terminate their participation in the study, according to the terms of the site contract. The Investigator/Sponsor should notify the IEC/IRB in writing of the trial's completion or early termination and send a copy of the notification to the Sponsor.

12.3 Study Documentation and Storage

An eCRF utilizing an Electronic Data Capture (EDC) application will be used for this study.

The Investigator should ensure that all appropriately qualified persons to whom he/she has delegated trial duties are recorded on a Sponsor-approved Delegation of Site Responsibilities Form.

Source documents are original documents, data, and records from which the patient's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, imaging, and correspondence. In this study, CRFs may not be used as source documents.

The Investigator and Study Center staffs are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation in accordance with Section 8 of the ICH Guidelines E6 (R2), suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Elements should include:

- Patient files containing completed CRFs, informed consents, and supporting copies of source documentation
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation and all correspondence to and from the IEC/IRB and the Sponsor
- If volanesorsen supplies are maintained at the Study Center, proof of receipt, volanesorsen Accountability Record, Return of volanesorsen for Destruction, final study volanesorsen reconciliation, and all volanesorsen-related correspondence

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

No study document should be destroyed without prior written agreement between the Sponsor or and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor.

12.4 Study Monitoring

The Sponsor representative and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the trial (e.g., CRFs and other pertinent data) provided that patient confidentiality is respected.

The Sponsor monitor is responsible for inspecting the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to patient medical records and other study-related records needed to verify the entries on the CRFs.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH E6 (R2) and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's Clinical Quality Assurance Department. Inspection of Study Center facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the trial conduct and compliance with the protocol, ICH E6 (R2), and applicable regulatory requirements.

To ensure the quality of clinical data a clinical data management review will be performed on patient data received by the Sponsor. During this review, patient data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or Study Center notifications will be sent to the Study Center for completion and return to Sponsor.

The Principal Investigator will sign and date the indicated places on the CRF. These signatures will indicate that the principal Investigator inspected or reviewed the data on the CRF, the data queries, and the Study Center notifications, and agrees with the content.

12.5 Language

Case report forms must be completed in English. Generic names for concomitant medications should be recorded in English if possible, unless it is a combination drug, then record the trade name in English.

All written information and other material to be used by patients and investigative staff must use vocabulary and language that are clearly understood.

12.6 Compensation for Injury

The Sponsor maintains appropriate insurance coverage for clinical trials and will follow applicable local compensation laws. Patients will be treated and/or compensated for any study-related illness/injury in accordance with the information provided in the Compensation for Injury section of the Informed Consent document.

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14. APPENDICES

Appendix A Schedule of Procedures

Qualification through Treatment Period

Post-Treatment Follow-up
(For patients not opting to participate in the Extended Treatment Period)

First 52-Week Extended Treatment Period

First 52-Week Extended Treatment Period Post-Treatment Follow-Up
(For patients not opting to participate in the second 52-Week Extended Treatment Period)

Second 52-Week Extended Treatment Period

Second 52-Week Extended Treatment Period Post-Treatment Follow-Up

Appendix A Schedule of Procedures – Qualification through Treatment Period

Study Period		Qual[a]	Treatment Period																						
Study Week		-2 to -1	Wk 1		Wk 4	Wk 6	Wk 8	Wk 10	Month 3		Wk 15 & 17	Wk 19	Wk 21 & 23	Month 6		Wk 28 & 30	Wk 32	Wk 34 & 36	Wk 38	Wk 40 & 42	Wk 44	Wk 46 & 48	Month 12	
									Wk 12	Wk 13				Wk 25	Wk 26								Wk 50	Wk 52 or ET
Study Day		-14 to -7	1	2	22	36	50	64	78	85	99 & 113	127	141 & 155	169	176	190 & 204	218	232 & 246	260	274 & 288	302	316 & 330	344	358
Visit Window+/- Days		0	0	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Informed Consent		X																						
Outpatient Visit		X	X	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X	X[j]	X[j]	X[j]	X[j]	X	X[j]	X[j]	X[j]	X	X[j]	X[j]	X[j]	X[j]	X
Inclusion/Exclusion Criteria		X																						
Medical History[q]		X																						
Vital Signs + body weight (+ height on Day 1 only)		X	X		X		X			X					X				X					X
Physical Examination		X	X							X					X				X					X
12- lead ECG (triplicate)		X								X					X				X					X
MRI (liver/spleen)		X																						X[k]
Echocardiography		X													X[k]									X[k]
Blood Draw (Fasting)[e]	Chemistry Panel	X	X		X		X			X		X			X		X		X		X			X
	CBC with Differential[b]	X	← Platelets are assessed each calendar week, visits do not have specified windows to allow flexibility of scheduling. →												X									
	Serum Lipid Panel	X	X		X		X		X	X				X	X				X				X	X
	Blood viscosity[r]		X							X					X									X
	Platelet aggregation[r]	X	X							X					X									X
	Coagulation (aPTT, PT, INR)	X					X			X					X				X					X
	hsCRP, HbA1c, FPG, and de-lipidated free glycerol	X[n]	X							X					X									X
	Sedimentation Rate		X							X					X									X
	Complement (C5a, Bb)		X							X					X									X
	Plasma PK - Volanesorsen		X[l]	X	X		X			X					X				X					X
	Anti-Volanesorsen Antibodies		X		X		X			X					X				X					X
	FSH (women only, if applicable)	X																						
	Serum Pregnancy Test[d]	X			X		X			X		X			X		X		X		X			X
	Archived Serum & Plasma Samples[e]		X				X			X					X									X
	Troponin I[o]	X																						
	Platelet Bound Autoantibodies[r]		X																					
	Archive blood sample for potential gene sequencing related to hypertriglyceridemia (Group 2 if not available from index study)[g]	X																						

Appendix A Schedule of Procedures - Qualification through Treatment Period *Continued*

Study Period	Qual[a]	Treatment Period																					
Study Week	-2 to -1	Wk 1		Wk 4	Wk 6	Wk 8	Wk 10	Month 3		Wk 15 & 17	Wk 19	Wk 21 & 23	Month 6		Wk 28 & 30	Wk 32	Wk 34 & 36	Wk 38	Wk 40 & 42	Wk 44	Wk 46 & 48	Month 12	
								Wk 12	Wk 13				Wk 25	Wk 26								Wk 50	Wk 52 or ET
Study Day	-14 to -7	1	2	22	36	50	64	78	85	99 & 113	127	141 & 155	169	176	190 & 204	218	232 & 246	260	274 & 288	302	316 & 330	344	358
Visit Window+/- Days	0	0	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Urinalysis[c]	X	X^m		X		X			X^m		X^m			X^m		X^m		X^m		X^m			X^m
Fundus Photography[f]	X																						X^k
Genetic testing for FCS diagnosis (if not available in medical history)[g]	X																						
Weekly Study Drug: SC Injection		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Symptom Diary (weekly)	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Assessment(s)		X							X					X									X
Food/Drink Diary (quarterly)[h]		X							X					X									X
Diet/Alcohol Counseling[i]	X	X		X		X			X					X				X					X
Adverse Events	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Appendix A Schedule of Procedures – Post-Treatment Follow-up (for patients not opting to participate in the Extended Treatment Period)

Study Period		Post Treatment Follow-up[p]				
Study Week		Wk 54 & 56	Wk 58	Wk 65	Wk 71	Wk 78
Study Day		372 & 386	400	449	491	540
Visit Window+/- Days		2	7	7	7	7
Outpatient Visit		X[j]	X[j]	X	X[j]	X
Vital Signs + body weight (+ height on Day 1 only)				X		X
Physical Examination				X		X
12- lead ECG (triplicate)				X		X
Blood Draw (Fasting)[c]	Chemistry Panel		X	X	X	X
	CBC with Differential[b]	X[s]	X	X	X	X
	Serum Lipid Panel			X		X
	hsCRP, HbA1c, FPG, and de-lipidated free glycerol			X		X
	Sedimentation Rate			X		X
	Complement (C5a, Bb)			X		X
	Plasma PK - Volanesorsen			X		X
	Anti-Volanesorsen Antibodies			X		X
	Serum Pregnancy Test[d]		X	X	X	X
	Archived Serum & Plasma Samples[e]			X		X
Urinalysis[c]			X[m]	X[m]	X[m]	X[m]
Symptom Diary (weekly)		X	X	X	X	X
Quality of Life Assessment(s)				X		X
Food/Drink Diary (quarterly)[h]				X		X
Diet/Alcohol Counseling[i]			X	X	X	X
Adverse Events		X	X	X	X	X
Concomitant Medication		X	X	X	X	X

Legend:

a Qualification procedures performed (Please refer to Sections 3.4, 4.1, and 6.1.2)

b Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1 week and the result must be reviewed by the Investigator and confirmed to be acceptable before treatment can continue. All platelet count results will be promptly reviewed by the Investigator to determine if the count has met a stopping rule, or the dose reduction rule of 100,000/mm^3, or the dose pause rule of 75,000/mm^3. Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor

c Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours. During treatment period urine and blood samples will be collected prior to Study Drug administration. Does not apply to 24-hour PK blood draw.

d Females of childbearing potential only

e Serum and plasma samples will be collected and stored for follow-up exploration of laboratory findings and/or adverse events (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.) in this or subsequent clinical studies of volanesorsen

f If possible, fundus photography should be completed prior to administration of the first dose of Study Drug (Group 2 ISIS 304801-CS16 roll over patients) and repeated at Week 52 (Please refer to Section 6.2.2.2)

g Genetic testing can be conducted for study Qualification (Group 2 ISIS 304801-CS16 roll over patients); genetic testing will only be conducted if allowed in the geographic region and only after the patient has given specific written informed consent for genetic testing. A blood sample for potential gene sequencing may be collected at timepoints other than Screening or Qualification Visits.

h In addition to diary, patients will be contacted at random times during the study to review their current eating and drinking habits

i To reinforce compliance to the diet and alcohol restrictions. Random diet/alcohol assessments (phone visits) will also be performed by dietician or study personnel

j Assessments and procedures to be conducted by either a home healthcare nurse, or the Study Center as arranged by the Study Center personnel

k A ± 7-day window is allowed for MRI, echocardiography procedures and fundus photography

l Full or abbreviated PK profile (see Appendix C)

m Expanded urinalysis (see Appendix B)

n HbA1c only

o All abnormal troponin samples will be rerun at the central laboratory and also analyzed for CK-MB

p If needed, the post-treatment follow-up period will be extended (with patients monitored every 6 weeks) until apoC-III levels return to baseline values

q Patient charts will be reviewed in order to collect data for events of acute pancreatitis or suspected pancreatitis in the patient's medical history. Chart review may be conducted at any time during the study. These events will be adjudicated in the same manner as for events of pancreatitis during the study

r May be done. Blood viscosity and platelet aggregation in volanesorsen-treatment naïve patients only

s Platelets are assessed each calendar week, visits do not have specified windows to allow flexibility of scheduling

Appendix A Schedule of Procedures – First 52-Week Extended Treatment Period

Study Period		Extended Treatment Period														
Study Week		**Wk 54 & 56**	**Wk 58**	**Wk 60 & 62**	**Mo 15 Wk 64**	**Wk 66 & 68**	**Wk 70**	**Wk 72 & 74**	**Mo 18 Wk 76**	**Wk 78 & 80**	**Wk 82**	**Wk 84, 86, & 88**	**Mo 21 Wk 90**	**Wk 92 & 94**	**Wk 96**	**Wk 98, 100 & 102**	**Mo 24 Wk 104**
Study Day		**372 & 386**	**400**	**414 & 428**	**442**	**456 & 470**	**484**	**498 & 512**	**526**	**540 & 554**	**568**	**582, 596 & 610**	**624**	**638 & 652**	**666**	**680, 694 & 708**	**722**
Visit Window+/- Days		**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
Outpatient Visit		X[f]	X[f]	X[f]	X	X[f]	X[f]	X[f]	X	X[f]	X[f]	X[f]	X	X[f]	X[f]	X[f]	X
Vital Signs (+ body weight)					X				X				X				X
Physical Examination									X								X
12- lead ECG (triplicate)									X								X
Urinalysis (including P/C ratio)			X		X		X		X		X		X		X		X
Blood Draw (Fasting)[b]	Chemistry Panel		X		X		X		X		X		X		X		X
	CBC with Differential[a]	X Platelets are assessed each calendar week, visits do not have specified windows to allow flexibility of scheduling.															
	Serum Lipid Panel				X				X				X				X
	Coagulation (aPTT, PT, INR)				X				X				X				X
	Troponin I				X				X				X				X
	Plasma PK - ISIS 304801[c]								X								X
	Anti-ISIS 304801 Antibodies								X								X
	Serum Pregnancy Test[d]		X		X		X		X		X		X		X		X
	Platelet Function[g]	X May be assessed at various timepoints, visits do not have specified windows to allow flexibility of scheduling.															
Weekly Study Drug: SC Injection		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Diet/Alcohol Counseling[e]					X				X				X				X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Legend:

a Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1 week and the result must be reviewed by the Investigator and confirmed to be acceptable before treatment can continue. All platelet count results will be promptly reviewed by the Investigator to determine if the count has met a stopping rule, or the dose reduction rule of 100,000/mm^3, or the dose pause rule of 75,000/mm^3. Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor

b Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours. During treatment period urine and blood samples will be collected prior to Study Drug administration

c Abbreviated PK collection (see Appendix C)

d Females of childbearing potential only

e To reinforce compliance to the diet and alcohol restrictions

f Assessments and procedures to be conducted by either a home healthcare nurse, or the Study Center as arranged by the Study Center personnel

g May be done

Appendix A Schedule of Procedures – First 52-Week Extended Treatment Period Post-Treatment Follow-Up (For patients not opting to participate in the second 52 Week Extended Treatment Period)

Study Period		Post Treatment Follow-up[a]				
Study Week		Wk 106 & 108	Wk 110	Wk 117	Wk 123	Wk 130
Study Day		736 & 750	764	813	855	904
Visit Window+/- Days		2	7	7	7	7
Outpatient Visit		X[b]	X[b]	X	X[b]	X
Vital Signs + body weight (+ height on Day 1 only)				X		X
Physical Examination				X		X
12- lead ECG (triplicate)				X		X
Blood Draw (Fasting)[e]	Chemistry Panel		X	X	X	X
	CBC with Differential[c]	X[d]	X	X	X	X
	Serum Lipid Panel			X		X
	hsCRP, HbA1c, FPG, and de-lipidated free glycerol			X		X
	Sedimentation Rate			X		X
	Complement (C5a, Bb)			X		X
	Plasma PK - Volanesorsen			X		X
	Anti-Volanesorsen Antibodies			X		X
	Serum Pregnancy Test[f]		X	X	X	X
	Archived Serum & Plasma Samples[g]			X		X
Urinalysis			X[h]	X[h]	X[h]	X[h]
Symptom Diary (weekly)		X	X	X	X	X
Quality of Life Assessment(s)				X		X
Diet/Alcohol Counseling[i]			X	X	X	X
Adverse Events		X	X	X	X	X
Concomitant Medication		X	X	X	X	X

Legend:

a If needed, the post-treatment follow-up period will be extended (with patients monitored every 6 weeks) until apoC-III levels return to baseline values

b Assessments and procedures to be conducted by either a home healthcare nurse, or the Study Center as arranged by the Study Center personnel

c Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1 week and the result must be reviewed by the Investigator and confirmed to be acceptable before treatment can continue. All platelet count results will be promptly reviewed by the Investigator to determine if the count has met a stopping rule, or the dose reduction rule of 100,000/mm^3, or the dose pause rule of 75,000/mm^3. Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor

d Platelets are assessed each calendar week, visits do not have specified windows to allow flexibility of scheduling

e Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours.

f Females of childbearing potential only

g Serum and plasma samples will be collected and stored for follow-up exploration of laboratory findings and/or adverse events (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.) in this or subsequent clinical studies of volanesorsen

h Expanded urinalysis (see Appendix B)

i To reinforce compliance to the diet and alcohol restrictions. Random diet/alcohol assessments (phone visits) will also be performed by dietician or study personnel

Appendix A Schedule of Procedures – Second 52-Week Extended Treatment Period

Study Period		**Extended Treatment Period**			
Study Week		**Wk 116**	**Mo 30 Wk 128**	**Mo 33 Wk 142**	**Wk 156**
Study Day		**806**	**890**	**988**	**1086**
Visit Window+/- Days		**2**	**2**	**2**	**2**
Outpatient Visit		X	X	X	X
Vital Signs (+ body weight)		X	X	X	X
Physical Examination			X		X
Urinalysis (including P/C ratio)		X	X	X	X
Blood Draw (Fasting)[b]	Chemistry Panel	X	X	X	X
	CBC with Differential[a]	◄—— Xe ——► Platelets are assessed each calendar week, visits do not have specified windows to allow flexibility of scheduling.			
	Serum Lipid Panel	X	X	X	X
	Serum Pregnancy Test[c]	X	X	X	X
	Anti-ISIS 304801 Antibodies				X
Weekly Study Drug: SC Injection		◄—— X ——►			
Diet/Alcohol Counseling[d]		X	X	X	X
Adverse Events		X	X	X	X
Concomitant Medication		X	X	X	X

Legend:

a Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1 week and the result must be reviewed by the Investigator and confirmed to be acceptable before treatment can continue. All platelet count results will be promptly reviewed by the Investigator to determine if the count has met a stopping rule, or the dose reduction rule of 100,000/mm^3, or the dose pause rule of 75,000/mm^3. Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor

b Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours. During treatment period urine and blood samples will be collected prior to Study Drug administration

c Females of childbearing potential only

d To reinforce compliance to the diet and alcohol restrictions

e Assessments and procedures to be conducted by either a home healthcare nurse, or the Study Center as arranged by the Study Center personnel

Appendix A Schedule of Procedures – Second 52-Week Extended Treatment Period Post-Treatment Follow-Up

Study Period		Post Treatment Follow-up[a]				
Study Week		**Wk 158 & 160**	**Wk 162**	**Wk 169**	**Wk 175**	**Wk 182**
Study Day		**1100 & 1114**	**1128**	**1177**	**1219**	**1268**
Visit Window+/- Days		**2**	**7**	**7**	**7**	**7**
Outpatient Visit		X[b]	X[b]	X	X[b]	X
Vital Signs + body weight (+ height on Day 1 only)				X		X
Physical Examination				X		X
12- lead ECG (triplicate)				X		X
Blood Draw (Fasting)[e]	Chemistry Panel		X	X	X	X
	CBC with Differential[c]	X[d]	X	X	X	X
	Serum Lipid Panel			X		X
	hsCRP, HbA1c, FPG, and de-lipidated free glycerol			X		X
	Sedimentation Rate			X		X
	Complement (C5a, Bb)			X		X
	Plasma PK - Volanesorsen			X		X
	Anti-Volanesorsen Antibodies			X		X
	Serum Pregnancy Test[f]		X	X	X	X
	Archived Serum & Plasma Samples[g]			X		X
Urinalysis			X[h]	X[h]	X[h]	X[h]
Symptom Diary (weekly)		X	X	X	X	X
Quality of Life Assessment(s)				X		X
Diet/Alcohol Counseling[i]			X	X	X	X
Adverse Events		X	X	X	X	X
Concomitant Medication		X	X	X	X	X

Legend:

a If needed, the post-treatment follow-up period will be extended (with patients monitored every 6 weeks) until apoC-III levels return to baseline values

b Assessments and procedures to be conducted by either a home healthcare nurse, or the Study Center as arranged by the Study Center personnel

c Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1 week and the result must be reviewed by the Investigator and confirmed to be acceptable before treatment can continue. All platelet count results will be promptly reviewed by the Investigator to determine if the count has met a stopping rule, or the dose reduction rule of 100,000/mm^3, or the dose pause rule of 75,000/mm^3. Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor

d Platelets are assessed each calendar week, visits do not have specified windows to allow flexibility of scheduling

e Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours

f Females of childbearing potential only

g Serum and plasma samples will be collected and stored for follow-up exploration of laboratory findings and/or adverse events (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.) in this or subsequent clinical studies of volanesorsen

h Expanded urinalysis (see Appendix B)

i To reinforce compliance to the diet and alcohol restrictions. Random diet/alcohol assessments (phone visits) will also be performed by dietician or study personnel

Appendix B List of Laboratory Analytes

Appendix B List of Laboratory Analytes

Based on emerging data from this or future studies, additional tests not listed below may be performed on stored samples to better characterize the profile of volanesorsen or other similar oligonucleotides.

Clinical Chemistry Panel

- Sodium
- Potassium
- Chloride
- Bicarbonate
- Total protein
- Albumin
- Calcium
- Magnesium
- Phosphorus
- Glucose
- BUN
- Creatinine
- Uric Acid
- Total bilirubin
- Direct (conjugated) bilirubin
- Indirect (unconjugated) bilirubin
- ALT
- AST
- Alkaline phosphatase

Coagulation

- aPTT (sec)
- PT (sec)
- INR

Lipid Panel

- Total Cholesterol
- LDL-C
- HDL-C
- Triglycerides
- Non-HDL-C
- VLDL-C
- apoA-1
- apoB
- apoC-III

Hematology

- Red blood cells
- Hemoglobin
- Hematocrit
- MCV, MCH, MCHC
- Platelets
- White blood cells
- WBC Differential (% and absolute)
  - Neutrophils
  - Eosinophils
  - Basophils
  - Lymphocytes
  - Monocytes

Pharmacokinetics[1] & Immunogenicity

- Volanesorsen levels in plasma
- Anti-volanesorsen antibodies in plasma

Other Assessments

- hsCRP
- Sedimentation Rate
- C5a, Bb
- Troponin I[2]
- CK-MB[2]
- Platelet Bound Autoantibodies[3]
- De-lipidated free glycerol
- HbA1c, FPG
- Blood viscosity[3]

Urinalysis

- Color
- Appearance
- Specific gravity
- pH
- Protein
- Blood
- Ketones
- Urobilinogen
- Glucose
- Bilirubin
- Leukocyte esterase
- Nitrate
- Microscopic examination[4]

Additional Measures for Expanded Urinalysis

- Total protein (quantitative)
- Microalbumin
- β2-microglobulin

Platelet Function

- Platelet aggregation[3]
- Platelet function[5]

1 Plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, IM testing (or possibly for purposes of IM assay development and/or validation), or to assess other actions of volanesorsen with plasma constituents

2 All abnormal troponin samples will be rerun at the central laboratory and also analyzed for CK-MB

3 May be done

4 Will be performed on abnormal findings unless otherwise specified

5 May be done using a point-of-care device on site

Appendix C Pharmacokinetic Sampling Schedule

Appendix C Pharmacokinetic Sampling Schedule

Blood samples for the determination of plasma volanesorsen concentrations will be collected prior to treatment, and at various times throughout the treatment and post-treatment follow-up period as noted in the tables below.

PK Sampling Schedule (All Patients except PK Subgroup)

Week	**Wk 1**	**Wk 4**	**Wk 8**	**Wk 13**	**Wk 26**	**Wk 38**	**Wk 52**	**Wk 65**	**Wk 78**
Study Day	**D1**	**D22**	**D50**	**D85**	**D176**	**D260**	**D358**	**D449**	**D540**
Visit Window +/- Days	0	2	2	2	2	3	2	7	7
Time Point	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime	Anytime

PK Sampling Schedule (PK Subgroup only*)

Week	**Wk 1**	**Wk 1**	**Wk 4**	**Wk 8**	**Wk 13**	**Wk 26**	**Wk 38**	**Wk 52**	**Wk 65**	**Wk 78**
Study Day	**D1**	**D2**	**D22**	**D50**	**D85**	**D176**	**D260**	**D358**	**D449**	**D540**
Visit Window +/- Days	0	0	2	2	2	2	3	2	7	7
Time Point	Pre-dose, 1, 2, 3, 4, 6, 8, and 12 hrs post-dose	24 hrs Post-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime	Anytime

* Patients at selected sites will be asked to participate in the extended 24-hour PK profile beginning on Study Day 1. Participation is optional

PK Sampling Schedule – First 52-Week Extended Treatment Period

Week	**Wk 76**	**Wk 104**	**Wk 117**	**Wk 130**
Study Day	**D526**	**D722**	**D813**	**D904**
Visit Window +/- Days	2	2	7	7
Time Point	Pre-dose	Pre-dose	Anytime	Anytime

PK Sampling Schedule – Second 52-Week Extended Treatment Period

Week	**Wk 169**	**Wk 182**
Study Day	**D1177**	**D1268**
Visit Window +/- Days	7	7
Time Point	Anytime	Anytime

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

The following grading recommendations for adverse events relating to lab test abnormalities are based upon the **Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010**

Adverse Event	Mild	Moderate	Severe
Hematology			
aPTT prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage
Eosinophils increased[†]	650 – 1,500 cell/mm^3	1,501 - 5,000 cell/mm^3	>5,000 cell/mm^3
Fibrinogen decreased	<1.0 - 0.75 x LLN or <25% decrease from baseline	<0.75 - 0.5 x LLN or 25 - <50% decrease from baseline	<0.5 x LLN or ≥50% decrease from baseline
Hemoglobin decreased (Anemia)	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated
Hemoglobin increased	Increase in >0 - 2 g/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 g/dL above ULN or above baseline if baseline is above ULN	Increase in >4 g/dL above ULN or above baseline if baseline is above ULN
INR increased	>1 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation
Lymphocyte count decreased	<LLN - 800/mm^3; <LLN - 0.8 x 10^9/L	<800 - 500/mm^3; <0.8 - 0.5 x 10^9 /L	<500 /mm^3; <0.5 x 10^9 /L
Lymphocyte count increased	-	>4000/mm^3 - 20,000/mm^3	>20,000/mm^3
Neutrophil count decreased	<LLN - 1500/mm^3; <LLN - 1.5 x 10^9 /L	<1500 - 1000/mm^3; <1.5 - 1.0 x 10^9 /L	<1000/mm^3; <1.0 x 10^9 /L
Platelet count decreased	<LLN - 75,000/mm^3; <LLN - 75.0 x 10^9 /L	<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9 /L	<50,000/mm^3; <50.0 x 10^9 /L
White blood cell decreased	<LLN - 3000/mm^3; <LLN - 3.0 x 10^9 /L	<3000 - 2000/mm^3; <3.0 - 2.0 x 10^9 /L	<2000/mm^3; <2.0 x 10^9 /L
Chemistry			
Acidosis	pH <normal, but **>=**7.3	-	pH <7.3
Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Alkalosis	pH >normal, but ≤7.5	-	pH >7.5
Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 x ULN
Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

Adverse Event	Mild	Moderate	Severe
Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer
CD4 lymphocytes decreased	<LLN - 500/mm^3; <LLN - 0.5 x 10^9 /L	<500 - 200/mm^3; <0.5 - 0.2 x 10^9 /L	<200/mm^3; <0.2 x 10^9 /L
CPK increased*	>ULN - <6 ULN	6 - 10 x ULN	>10 x ULN
Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 x ULN
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 mg/dL; >3.1 mmol/L; Ionized calcium >1.6 mmol/L; hospitalization indicated
Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 mg/dL; >13.9 mmol/L; hospitalization indicated
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0; hospitalization indicated
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 mg/dL; >1.23 mmol/L
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 mmol/L; hospitalization indicated
Hyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 mg/dL; <1.75 mmol/L; Ionized calcium <0.9 mmol/L; hospitalization indicated
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 mg/dL; <3.0 mmol/L	<40 mg/dL (<2.2 mmol/L) AND requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions‡
Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 mmol/L; hospitalization indicated
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 mg/dL; <0.4 mmol/L
Hyponatremia	<LLN - 130 mmol/L	-	<130 mmol/L
Hypophosphatemia	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 mg/dL; <0.6 mmol/L
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

Adverse Event	Mild	Moderate	Severe
Urine			
Proteinuria Adults	1+ proteinuria; urinary protein <1.0 g/24 hrs	2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs;	Urinary protein ≥3.5 g/24 hrs;
Children	-	Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Urine P/C >1.9
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated

†Grading for this parameter is derived from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007

*Grading for this parameter is derived from the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0, Nov 2014

‡Modified for consistency with the ADA and Endocrine Society Guidelines (Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. Diabetes Care 2013;36:1384-95)

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ISIS 304801-CS7

The APPROACH Open-Label Study

Volanesorsen (ISIS 304801)

An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol Amendment 9 - France – 25 May 2018

EudraCT No: 2015-003755-21

ISIS 304801-CS7

The APPROACH Open-Label Study

Volanesorsen (ISIS 304801)

An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol Amendment 9 - France – 25 May 2018

Protocol History:

Original Protocol: 28 August 2015
Protocol Amendment 1: 2 February 2016
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Protocol Amendment 4: 6 June 2016
Protocol Amendment 5: 19 August 2016
Protocol Amendment 6: 16 September 2016
Protocol Amendment 7: 3 February 2017
Protocol Amendment 8: 10 April 2017

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Protocol Number: ISIS 304801-CS7

Protocol Amendment 9 - France

EudraCT No: 2015-003755-21

Clinical Phase: 3

The APPROACH Open-Label Study

Volanesorsen (ISIS 304801)

An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

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Date: 25 May 2018

Confidentiality Statement

This document contains confidential information of Akcea Therapeutics, Inc., that must not be disclosed to anyone other than the recipient study staff and members of the independent ethics committee, institutional review board, or authorized regulatory agencies. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Akcea Therapeutics, Inc.

Protocol Signature Page

Protocol Number:	ISIS 304801-CS7
Protocol Title:	An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Amendment:	Amendment 9 - France
Date:	25 May 2018

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)", dated 25 May 2018, and agree to conduct the study as described herein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice E6 (R2).

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Akcea Therapeutics, Inc.

Investigator's Signature

Investigator's Name *(please print)*

Date (DD Month YYYY)

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PROTOCOL AMENDMENT

Protocol Number: ISIS 304801-CS7

Protocol Title: An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Amendment Number: 9 - France

Amendment Date: 25 May 2018

The purpose of this protocol amendment is to implement the following modifications to Protocol ISIS 304801-CS7 Amendment 8 dated 10 April 2017:

1. To prolong the extended treatment period an additional 52 weeks.

Minor changes (not included in the list of changes below) have been made throughout the protocol to correct errors and/or to improve the overall clarity of the original protocol but these changes do not impact subject safety, exposure, or the overall study design.

The following table provides a summary list of major changes to the protocol, additions are indicated as underline and deletions are indicated as strikethrough:

Protocol Section	Description of Change	Rationale
Protocol Synopsis: Study Design and Study Visit Schedule and Procedures 3.1 Study Design 3.4.3 Extended Treatment Period	Following the Week 52 visit, patients will ~~enter an at least 26-week post-treatment evaluation period or will participate in an expanded access program pending approval by the IRBs/IEC, and the appropriate regulatory authorities.~~ have the option to continue dosing for up to an additional 52 weeks for a total of 104 weeks of dosing. Patients not continuing dosing will enter a 26-week post-treatment follow-up period.	To allow patients the option of continuing treatment with volanesorsen after completion of the 52-week open-label treatment period.
Protocol Synopsis: Study Visit Schedule and Procedures	○ ~~An at least 26-week post-treatment evaluation period~~ Option to participate in an extended treatment period (up to an additional 52 weeks) ○ A 26-week post-treatment follow-up period	To allow patients the option of continuing treatment with volanesorsen after completion of the 52-week open-label treatment period. For patients continuing

		treatment up to 104 weeks, the 26-week post-treatment follow-up period has been added for those patients also.
Section 6.1.3 Extended Treatment Period	After completion of the Week 52 visit assessments, patients will have the option of continuing dosing for up to an additional 52 weeks. During the extended treatment period, patients will have assessments and procedures done during Weeks 54-104 as per the Schedule of Procedures in Appendix A. Assessments and procedures may be conducted by either a home healthcare service or the Study Center, however the patient will be required to visit the study center approximately every 3 months. Study Drug will be administered once weekly unless the patient is on a biweekly dosing schedule for safety reasons (Section 8.1). Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), AEs, concomitant medication/procedure information, lipid panel, volanesorsen plasma concentrations, IM testing, ECGs, and physical examinations will be performed according to the Schedule of Procedures in Appendix A. Adverse events at the injection site should be collected as adverse events. Dietary counseling will be reinforced at intervals throughout the extended treatment period. All blood and urine samples should be collected prior to volanesorsen administration. Blood sampling at Weeks 53, 54, 55, 56, 57, 58, 59, 60, 61, 62,63, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, and 103 may be conducted by a home healthcare nurse. Approval for study procedures to be conducted by a home healthcare nurse on other outpatient visit days will require prior approval by the Sponsor. Patients must be fasted prior to drawing all blood samples and samples drawn locally should also be sent to the central laboratory for analysis whenever possible. Dosing instructions and training will be provided to the patient where applicable.	To outline the procedures to be performed during the extended treatment period and 26-week post follow up treatment period. The extended treatment period provides additional volanesorsen dose exposure and patient safety evaluations.
Section 6.1.5	After completion of the Week 52 visit assessments, patients will have the option of continuing dosing for up to an additional 52 weeks as described in Section 6.1.3. Patients not continuing dosing will enter the 26-week post-treatment follow-up. ~~After completion of the Week 52 visit assessments, patients will enter the at least 26-week post-treatment evaluation period or will participate in an expanded access program pending approval by the IRBs/IEC, and the appropriate regulatory authorities.~~ The 26-week ~~period~~ post-treatment follow-up consists of at least 9 Study Center visits on Weeks 53, 54, 55, 56, 57, 58, 65, 71, and 78 (Weeks 53, 54, 55, 56, 57, 58, and 71 may be conducted by a home healthcare nurse). An additional 26-week post-treatment follow-up occurs after the extended treatment period with at least 9 Study Center visits on Weeks 105, 106, 107, 108, 109, 110, 117, 118, and 125 (Weeks 105, 106, 107, 108, 109, 110, and 118 may be conducted by a home healthcare nurse. These visits~~, as~~ are outlined in the Schedule of Procedures in Appendix A.	To outline the procedures to be performed during the extended treatment period and 26-week post follow up treatment period.

Appendix A Schedule of Procedures—Post-Treatment Follow-Up	**Study Period**		**Post Treatment Follow-up[p]**					Removed assessments that were not conducted during the post-treatment follow-up.
	Study Week		**Wk 54 & 56**	**Wk 58**	**Wk 65**	**Wk 71**	**Wk 78**	
	Study Day		**372 & 386**	**400**	**449**	**491**	**540**	
	Visit Window+/- Days		**2**	**7**	**7**	**7**	**7**	
	~~Informed Consent~~							
	Outpatient Visit		X[j]	X[j]	X	X[j]	X	
	~~Inclusion/Exclusion Criteria~~							
	Vital Signs + body weight (+ height on Day 1 only)				X		X	
	Physical Examination				X		X	
	12- lead ECG (triplicate)				X		X	
	~~MRI (liver/spleen)~~							
	~~Echocardiography~~							
	Blood Draw (Fasting)[c]	Chemistry Panel		X	X	X	X	
		CBC with Differential[b]	X[s]	X	X	X	X	
		Serum Lipid Panel			X		X	
		hsCRP, HbA1c, FPG, and de-lipidated free glycerol			X		X	
		Sedimentation Rate			X		X	
		Complement (C5a, Bb)			X		X	
		Plasma PK - Volanesorsen			X		X	
		Anti-Volanesorsen Antibodies			X		X	
		Serum Pregnancy Test[d]		X	X	X	X	
		Archived Serum & Plasma Samples[e]			X		X	
	Urinalysis[c]			X[m]	X[m]	X[m]	X[m]	
	~~Fundus Photography~~[f]							
	~~Genetic testing for FCS diagnosis (if not available in medical history)~~[g]							
	~~Weekly Study Drug: SC Injection~~							
	Symptom Diary (weekly)		X	X	X	X	X	
	Quality of Life Assessment(s)				X		X	
	Food/Drink Diary (quarterly)[h]				X		X	

	Diet/Alcohol Counseling[i]		X	X	X	X	
	Adverse Events	X	X	X	X	X	
	Concomitant Medication	X	X	X	X	X	
Appendix A: Schedule of Procedures—Extended Treatment Period	A Schedule of Procedures table was added for the 52 week extended treatment period.						Schedule of procedures table added for the 52-week extended treatment period.

Appendix A: Schedule of Procedures—Extended Treatment Period Post-Treatment Follow-Up

Study Period		Post Treatment Follow-up[a]				
Study Week		**Wk 106 & 108**	**Wk 110**	**Wk 117**	**Wk 123**	**Wk 130**
Study Day		**736 & 750**	**764**	**813**	**855**	**904**
Visit Window+/- Days		**2**	**7**	**7**	**7**	**7**
Outpatient Visit		X[b]	X[b]	X	X[b]	X
Vital Signs + body weight (+ height on Day 1 only)				X		X
Physical Examination				X		X
12- lead ECG (triplicate)				X		X
Blood Draw (Fasting)[e]	Chemistry Panel		X	X	X	X
	CBC with Differential[c]	X[d]	X	X	X	X
	Serum Lipid Panel			X		X
	hsCRP, HbA1c, FPG, and de-lipidated free glycerol			X		X
	Sedimentation Rate			X		X
	Complement (C5a, Bb)			X		X
	Plasma PK - Volanesorsen			X		X
	Anti-Volanesorsen Antibodies			X		X
	Serum Pregnancy Test[f]		X	X	X	X
	Archived Serum & Plasma Samples[g]			X		X
Urinalysis			X[i]	X[i]	X[i]	X[i]
Symptom Diary (weekly)		X	X	X	X	X
Quality of Life Assessment(s)				X		X
Diet/Alcohol Counseling[i]			X	X	X	X

Schedule of procedures table added for 26 week post treatment follow-up subsequent to the 52 week extended treatment period.

		Adverse Events	X	X	X	X	X		
		Concomitant Medication	X	X	X	X	X		

Appendix C: Pharmacokinetic Sampling Schedule		**Week**	**Wk 76**	**Wk 104**	**Wk 117**		A PK sampling scheduled was added for the 52 week extended treatment period.
		Study Day	**D526**	**D722**	**D813**		
		Visit Window +/- Days	2	2	7		
		Time Point	Pre-dose	Pre-dose	Anytime		

PROTOCOL SYNOPSIS

Protocol Title	An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Study Phase	3
Indication	Familial Chylomicronemia Syndrome
Study Objectives	To evaluate the safety and efficacy of dosing and extended dosing with volanesorsen (volanesorsen sodium 300 mg) in patients with FCS
Study Design	This is a multi-center open-label study of: Group 1: ISIS 304801-CS6 (index study) roll over FCS patients Group 2: ISIS 304801-CS16 (index study) roll over FCS patients All patients will receive volanesorsen 300 mg once per week for 52 weeks. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period. Following the Week 52 visit, patients will have the option to continue dosing for up to an additional 52 weeks for a total of 104 weeks of dosing. Patients not continuing dosing will enter a 26-week post-treatment follow-up period.
Number of Patients	Up to approximately 70 patients dosed
Study Population	Inclusion Criteria: 1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law 2. Age ≥ 18 years at time of informed consent 3. Groups 1 and 2: Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement. Group 2: Patients who enrolled in ISIS 304801-CS16 must also meet the following criteria in order to enter into the open-label study: a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L) b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) supported by documentation of at least 1 of the following: • Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1) • Post heparin plasma LPL activity of ≤ 20% of normal in medical history. Note: testing of LPL activity should not be performed to confirm eligibility for the study c. Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 index study 4. Able and willing to participate in a 78-week study
Study Population *Continued*	Inclusion Criteria: *Continued*

	Inclusion Criteria: *Continued* 5. Satisfy 1 of the following: a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved), abstinent*, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration b. Males: Surgically sterile, abstinent* or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration * Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception Exclusion Criteria: 1. Diabetes mellitus with any of the following: a. Newly diagnosed within 12 weeks of Qualification b. HbA1c ≥ 9.0% at Qualification c. Recent change in anti-diabetic pharmacotherapy (change in dosage or addition of new medication within 12 weeks of Qualification [with the exception of ± 10 units of insulin]) d. Anticipated need to change dose or type of medication during the treatment period of the Study (with the exception of ± 10 units of insulin) e. Current use of GLP-1 agonists 2. Severe hypertriglyceridemia other than due to familial chylomicronemia syndrome 3. Active pancreatitis within 4 weeks prior to Qualification 4. History within 6 months of Qualification of acute or unstable cardiac ischemia (myocardial infarction, acute coronary syndrome, new onset angina), stroke, transient ischemic attack or unstable congestive cardiac failure requiring a change in medication or major surgery within 3 months of Qualification

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	Exclusion Criteria: *Continued* 5. Any of the following laboratory values at Qualification a. Hepatic: • Total bilirubin > upper limit of normal (ULN), unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL • ALT > 2.0 x ULN • AST > 2.0 x ULN b. Renal: • Persistently positive (2 out of 3 consecutive tests ≥ 1+) for protein on urine dipstick. In the event of a positive test eligibility may be confirmed by a quantitative total urine protein measurement of < 500 mg/24 hrs • Persistently positive (2 out of 3 consecutive tests ≥ trace positive) for blood on urine dipstick. In the event of a positive test eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field • Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault < 50 mL/min (MDRD or CKD-EPI formulas can be used instead of Cockcroft-Gault for estimation of GFR in patients with low body weight after discussion with Sponsor Medical Monitor) c. Cardiac Troponin I > ULN at Qualification d. LDL-C > 130 mg/dL at Qualification e. Any other laboratory abnormalities which, in the opinion of the Investigator or the Sponsor, would make the patient unsuitable for inclusion 6. Uncontrolled hypertension (BP > 160/100 mm Hg) 7. History of thrombocytopenia (platelet count < 100,000/mm^3) or bleeding diathesis or coagulopathy or clinically-significant abnormality in coagulation parameters at Qualification 8. History of heart failure with NYHA greater than Class II 9. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1 10. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B 11. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated 12. Treatment with another investigational drug, biological agent, or device within 1 month of Qualification, or 5 half-lives of investigational agent, whichever is longer 13. Unwilling to comply with lifestyle requirements (Section 6.3)

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	Exclusion Criteria: *Continued* 14. Use of any of the following: a. Statins, omega-3 fatty acids (prescription and OTC), or fibrates unless on a stable dose for at least 3 months prior to Qualification and dose and regimen expected to remain constant during the treatment period. Patients taking OTC omega-3 fatty acids should make every effort to remain on the same brand throughout the study b. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to Qualification c. Systemic corticosteroids or anabolic steroids within 6 weeks prior to Qualification unless approved by the Sponsor Medical Monitor d. Atypical antipsychotic medications (e.g., olanzapine and clozapine) unless on a stable dose for at least 3 months prior to Qualification and dose and regimen expected to remain stable throughout the study e. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to Qualification and dose and regimen expected to remain constant during the treatment period f. Glybera gene therapy within 2 years prior to Qualification g. Oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, and apixaban) unless on a stable dose for at least 4 weeks prior to Qualification and regular clinical monitoring is performed h. Tamoxifen, estrogens or progestins unless on a stable dose for at least 4 months prior to Qualification and dose and regimen expected to remain constant during the treatment period i. Plasma apheresis within 4 weeks prior to Qualification or planned during the study j. Prior exposure to ISIS 304801 k. Any other medication unless stable at least 4 weeks prior to Qualification (Occasional or intermittent use of over-the-counter medications will be allowed at Investigator's discretion) 15. Blood donation of 50 to 499 mL within 30 days of Qualification or of > 499 mL within 60 days of Qualification 16. Known hypersensitivity to any of the excipients of the Study Drug (ISIS 304801 or placebo) 17. Have any other conditions, including new or worsening of existing condition, which, in the opinion of the Investigator or the Sponsor would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the study
Treatment Group	Volanesorsen 300 mg once per week
Study Drug Administration	Volanesorsen will be administered as subcutaneous (SC) injections.
Dose Adjustments	Dose adjustments, including dose interruptions and/or decreasing the dose frequency will be allowed for safety or tolerability after consultation with the Sponsor Medical Monitor.

PROTOCOL SYNOPSIS *Continued*

Rationale for Dose and Schedule Selection	The dose of 300 mg once weekly was chosen for the double-blinded placebo-controlled Phase 3 index studies (ISIS 304801-CS6 and ISIS 304801-CS16) based on the pharmacodynamic and safety analysis of the Phase 2 studies (Section 2.4) which included a subset of patients with FCS. The same dose of 300 mg once weekly will be used in this open-label study of FCS patients.

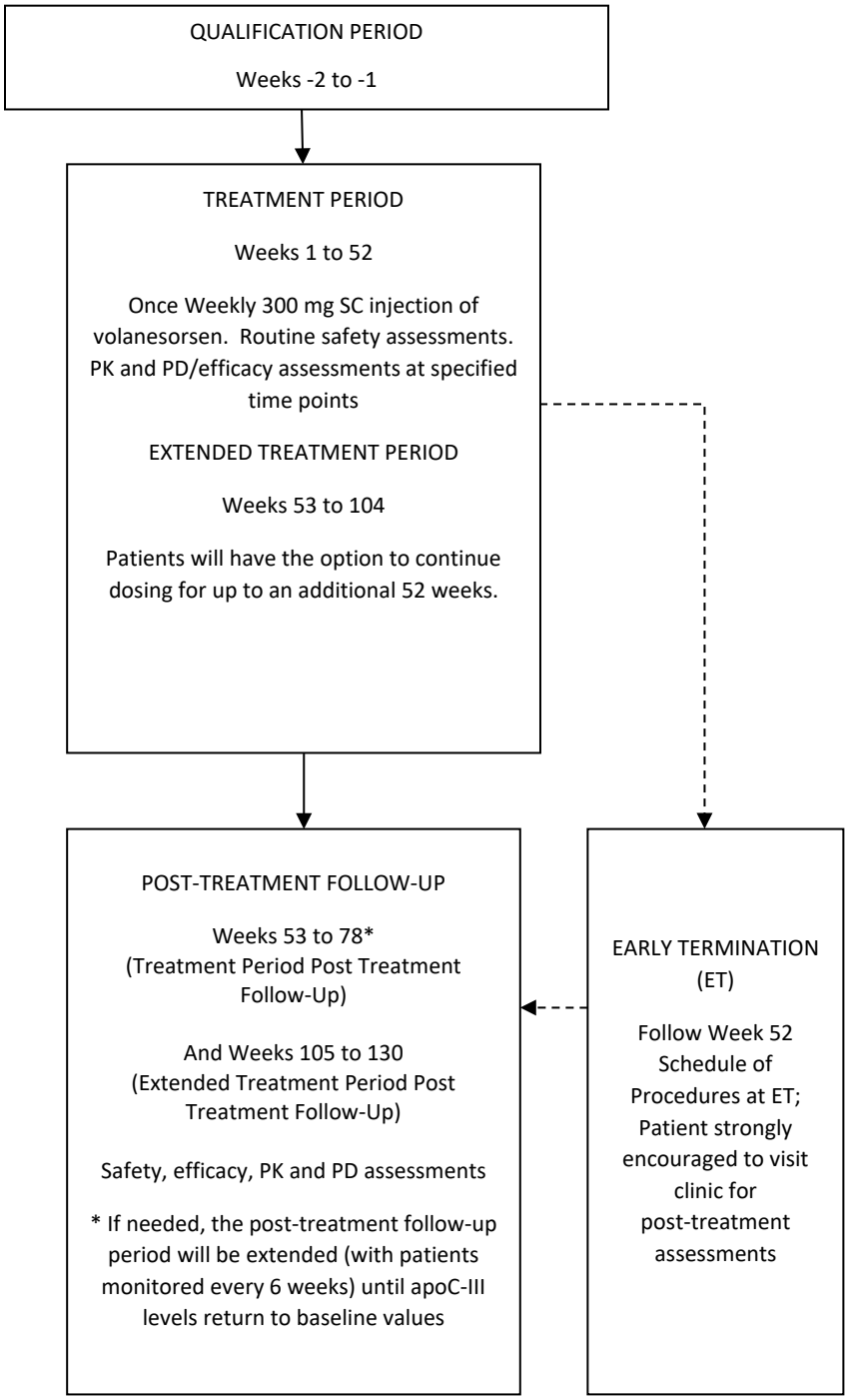
Study Visit Schedule and Procedures	The study for an individual patient will generally consist of the following periods:
	• A qualification period of up to 2 weeks (unless approved by the Sponsor). Please refer to Section 4.1 and Appendix A
	  ○ A 52-week treatment period during which volanesorsen will be administered as a once weekly SC injection
	  ○ Option to participate in an extended treatment period (up to an additional 52 weeks)
	  ○ A 26-week post-treatment follow-up period
	The patients, Investigators, study staff, and the Sponsor will remain blinded to lipid data through the last patient's Week 13 visit of the open-label study or until results from the database locks for the ISIS 304801-CS6 and ISIS 304801-CS16 index studies becomes available, whichever comes first.
	Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), adverse events (AE), concomitant medication/procedure information, lipid panel, blood viscosity, volanesorsen plasma concentrations, immunogenicity (IM) testing, platelet aggregation, liver/spleen magnetic resonance imaging (MRI), ECGs, echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Dietary counseling will be repeated at intervals throughout the treatment and follow-up period and a daily food/drink diary will be completed for the week prior to each quarterly visit by each patient. Following the Week 52 visit, patients will have the option to continue dosing for up to an additional 52 weeks. Patients not to continuing dosing will enter a 26-week post-treatment follow-up period.

Safety and Tolerability Evaluations	Overall safety and tolerability of volanesorsen will be assessed by determining the incidence and severity of adverse and serious adverse events (including independently adjudicated events of acute pancreatitis and MACE), withdrawals due to adverse events, and changes in laboratory and other safety parameters.

PROTOCOL SYNOPSIS *Continued*

Planned Analyses	Safety Endpoints: • Adverse events including adjudicated events of acute pancreatitis and MACE • Vital signs and weight • Physical examinations • Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis) • Echocardiography • Electrocardiograms (ECGs) • Use of concomitant medications • MRIs • Platelet aggregation (may be evaluated) Efficacy Endpoints: • Percent change and absolute change from baseline in fasting TG • Frequency and severity of patient reported abdominal pain during the treatment period • Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-high-density lipoprotein-cholesterol (non-HDL-C), apolipoprotein B [apoB], high-density lipoprotein-cholesterol (HDL-C), apolipoprotein A-1 [apoA-1], very-low-density lipoprotein-cholesterol (VLDL-C), and LDL-C • Percent change from baseline in fasting total apolipoprotein C-III (apoC-III) • Change in blood viscosity (may be evaluated) • Quality of Life questionnaires (EQ-5D, SF-36) • Adjudicated acute pancreatitis event rate • Other symptoms: eruptive xanthoma, lipemia retinalis
Pharmacokinetic Evaluations	Plasma samples will be taken from all patients for the measurement of volanesorsen as follows: trough levels (pre-dose) throughout treatment and post-treatment levels during the post-treatment follow-up period. In a subset of patients, more frequent assessment of plasma concentrations of volanesorsen will be performed to determine volanesorsen pharmacokinetic parameters. Plasma sample collection time points are detailed in Appendix A and Appendix C.
Statistical Considerations	No sample size calculations were performed as this is an open-label study.
Sponsor	Akcea Therapeutics, Inc.
Collaborator	Ionis Pharmaceuticals, Inc.

STUDY DESIGN AND TREATMENT SCHEMA



STUDY GLOSSARY

Abbreviation/Acronym	Definition
ADA	anti-drug antibody
AE	adverse Event
ALP	alkaline Phosphatase
ALT	alanine Aminotransferase
ANA	antinuclear Antibody
apoA-1	apolipoprotein A-1
apoB	apolipoprotein B
apoC-III	apolipoprotein C-III
apoE	apolipoprotein E
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
CBC	complete blood count
C_{max}	maximum observed drug concentration
CRF	case report form
DNA	deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
ET	early termination
FAS	full analysis set
FCS	Familial Chylomicronemia Syndrome
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
GPIHBP1	Glycosylphosphatidylinositol-anchored HDL-binding Protein 1
HAPI	Heritability and Phenotype Intervention
HbA1c	Glycated Hemoglobin
HDL	High-Density Lipoprotein
HDL-C	High-Density Lipoprotein-Cholesterol
hsCRP	High-sensitivity C-reactive protein
ICH	International Conference on Harmonization
IDL	Intermediate density lipoprotein
IEC	Independent Ethics Committee
IM	immunogenicity
Index Studies	ISIS 304801-CS6 and ISIS 304801-CS16

Abbreviation/Acronym	**Definition**
INR	International Normalized Ratio
IRB	Institutional Review Board
IXRS	Interactive Voice/Web-Response System
LDL	Low-Density Lipoprotein
LDL-C	Low-Density Lipoprotein-Cholesterol
LMF1	Lipase Maturation Factor 1
LPL	Lipoprotein Lipase
MACE	Major Acute Cardiovascular Event
MOE	2′-*O*-(2-methoxyethyl)
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NCS	not clinically-significant
NOAEL	No-Observed-Adverse-Effect Level
non-HDL-C	Non-High-Density Lipoprotein-Cholesterol
OTC	over the counter
PFS	prefilled syringe
PD	pharmacodynamic
PK	pharmacokinetic
PPS	per protocol set
PT	prothrombin time
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SUSAR	suspected unexpected serious adverse reaction
T2DM	type 2 diabetes mellitus
T_{max}	time to maximal concentration
TG	triglycerides
Treatment-emergent	occurring after first dose of Study Drug
TRL	Triglyceride-Rich Lipoproteins
ULN	upper limit of normal
VLDL	Very-Low-Density Lipoprotein
VLDL-C	Very-Low-Density Lipoprotein-Cholesterol
VLDL-TG	Lipoprotein-Triglyceride
WMA	World Medical Association

1. OBJECTIVES

The objective of the study is to evaluate the safety and efficacy of dosing and extended dosing with volanesorsen in patients with familial chylomicronemia syndrome.

2. BACKGROUND AND RATIONALE

2.1 Overview of Disease

Familial Chylomicronemia Syndrome (FCS) is an inherited disease characterized by severe hypertriglyceridemia and chylomicronemia, and risk or history of pancreatitis. It is a rare autosomal recessive disease that can be diagnosed either in childhood or adulthood.

Fasting plasma triglyceride (TG) levels in FCS patients are typically 10-fold to 100-fold above normal (1,500 to 15,000 mg/dL), despite extreme dietary fat restriction (20 g or approximately 15-20% of daily calorie intake) (Brunzell 1999-2011). Patients with FCS often present in infancy or childhood with frequent and severe abdominal pain, repetitive colicky pain, repeated episodes of potentially fatal acute pancreatitis, and failure to thrive (Brunzell 1999-2011; Tremblay et al. 2011). Physical examination frequently reveals eruptive xanthomas, lipemia retinalis and hepatosplenomegaly, and plasma from patients appears lactescent, interfering with determination of other laboratory parameters (Tremblay et al. 2011).

Patients with fasting triglyceride levels > 10 mmol/L probably have a component of chylomicronemia. Clinical diagnosis would include evidence of clinical features of chylomicronemia syndrome and secondary causes such as uncontrolled type 1 or type 2 diabetes mellitus (T2DM), hypothyroidism, poor diet, alcohol use, nephrotic syndrome or use of associated medications should be ruled out. The diagnosis of FCS may be made more specifically by genotyping or confirmation of very low or absent lipoprotein lipase (LPL) enzyme activity in post heparin plasma (Brunzell 1999-2011).

Patients with FCS carry a heavy burden of medical complications, the most serious, as described above, being an extreme risk of recurrent and potentially fatal pancreatitis. Due to the recurrent episodes of acute pancreatitis, these patients may also develop chronic pancreatitis and signs of exocrine or endocrine pancreatic insufficiency, including diabetes mellitus (Gaudet et al. 2013). While the pathophysiology underlying chylomicron-related pancreatitis has not been completely elucidated, 1 hypothesis is that large chylomicrons lodged in pancreatic capillaries are exposed to pancreatic lipase, with the subsequent release of free fatty acids through the hydrolysis of chylomicron-associated TGs. High concentrations of free fatty acids are thought to damage pancreatic cells leading to emergent pancreatitis (Yang et al. 2009; Berglund et al. 2012).

The etiology of extreme hypertriglyceridemia in FCS is considered to be ineffective triglyceride clearance, due to an extremely low level of LPL activity. LPL normally functions to hydrolyze triglycerides (TG) in chylomicrons along the luminal surface of capillaries, mainly in heart, skeletal muscle, and adipose tissue, promoting triglyceride clearance from the circulation. LPL is regulated by a number of key genes, and loss-of-function mutations in one of these genes, or the LPL gene itself, results in FCS (Surendran et al. 2012). In addition to loss of function mutations, null mutations, and nonsense mutations in the LPL gene, other genes currently identified in FCS patients, and known to directly influence LPL activity include: apolipoprotein C-II (APOC2) a cofactor for LPL (Schuster et al. 2011); apolipoprotein A-V (APOA5) an enhancer of LPL activity (Schaap et al. 2004); lipase maturation Factor 1 (LMF1), a transmembrane protein involved in LPL maturation (Doolittle et al. 2009);

glycosylphosphatidylinositol-anchored HDL-binding protein 1 (GPIHBP1), a capillary endothelial cell protein that provides a platform for LPL-mediated processing of chylomicrons (Beigneux et al. 2007).

2.2 Therapeutic Rationale

Apolipoprotein C-III (ApoC-III), a key regulator of plasma triglyceride levels, is a 79 amino acid glycoprotein synthesized principally in the liver (Ooi et al. 2008; Figure 1). ApoC-III is a major regulator of lipoprotein metabolism and plays a pivotal role in regulating plasma TG levels (Chan et al. 2008). It is a component of triglyceride-rich lipoproteins (TRLs) and a potent inhibitor of LPL (Lemieux et al. 2003). At higher concentrations apoC-III also inhibits hepatic lipase activity (Kinnunen and Ehnolm 1976), an enzyme which plays an important role in the conversion of dense very-low-density lipoprotein (VLDL) to intermediate density lipoprotein (IDL) and to LDL (Mendivil et al. 2010), as well as in the remodeling of HDL (Brown et al. 2010). In addition, increased apoC-III content adversely affects apoE-mediated hepatic uptake of TG-rich remnants (Mann et al. 1997). Thus, elevated plasma apoC-III levels are associated with impaired hydrolysis and retarded clearance of TG-rich particles, resulting in the accumulation of lipoprotein-triglyceride (VLDL-TG) and chylomicrons in plasma and the development of hypertriglyceridemia (Ito et al. 1990).

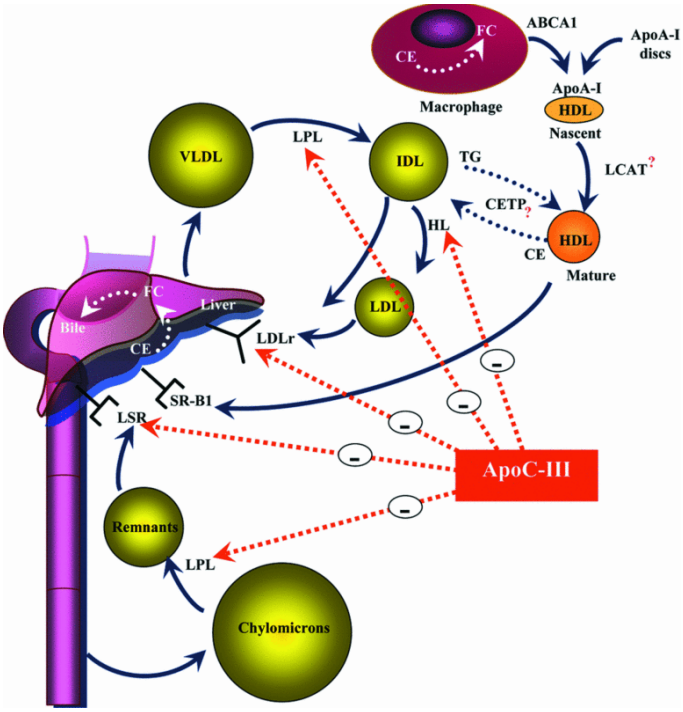


Figure 1 ApoC-III Regulates Lipoprotein Metabolism by Multiple Mechanisms

From Ooi et al. 2008; ABCA1 = ATP-binding cassette A1, apo = apolipoprotein, CE = cholesterol ester, CETP = cholesterol ester transfer protein, FC = free cholesterol, HDL = high-density lipoprotein, HL = hepatic lipase, IDL = intermediate-density lipoprotein, LCAT = lecithin cholesterol acyltransferase, LDL = low-density lipoprotein, LDLr = LDL receptor, LPL = lipoprotein lipase, LSR = lipolysis-stimulated receptor, SR-B1 = scavenger receptor B-1, TG = triglyceride, VLDL = very low-density lipoprotein.

Mechanistically, FCS is primarily a consequence of ineffective clearance of TRL. ApoC-III is a prominent component of TRL (e.g., VLDL and chylomicrons). In addition to its role in inhibiting LPL,

apoC-III inhibits TRL remnant (TG-depleted remnant lipoprotein) uptake by hepatic lipoprotein receptors by steric inhibition of the interaction of apoE with these receptors.

Human genetic data have demonstrated positive phenotypic associations with loss (e.g., null or nonsense mutations) and negative effects with gain of function mutations (Atzmon et al. 2006; Pollin et al. 2008; Petersen et al. 2010). A novel nonsense mutation in the apoC-III gene was identified in the heritability and phenotype intervention (HAPI) heart study in Old Order Amish that results in lower plasma apoC-III and TG levels and lower LDL-C, increased HDL-C and reduced atherosclerosis (Pollin et al. 2008). In another study involving a group of 214 Ashkenazi Jews of advanced age (had passed or nearly reached 100 years of age), genotype analysis revealed a polymorphism in the apoC-III gene (APOC3-641CC genotype) with a clear pattern of age-dependent frequency that was associated with significantly lower levels of apoC-III protein, a favorable lipoprotein profile and increased longevity (Atzmon et al. 2006). In contrast to the Amish and Ashkenazi apoC-III polymorphisms associated with lower plasma TG, apoC-III polymorphisms associated with higher plasma TG have also been recently described (Petersen et al. 2010). In a cohort of lean (mean body mass index [BMI] = 24.7 ± 3.6 kg/m^2) Asian Indians, carriers of apoC-III variant alleles (C-482T, T-455C, or both) were noted to have significantly higher plasma apoC-III and TG levels, and decreased ability to clear postprandial plasma TG from the circulation. Taken together, the available data strongly support the development of a therapy that reduces plasma apoC-III levels in order to reduce the very high circulating triglyceride and chylomicron levels that are accompanied by increasing risk for acute pancreatitis.

Given the profound reductions in TGs observed with volanesorsen treatment in FCS patients who have no detectable LPL activity (See Section 2.3.4), and the mechanistic data available to date on apoC-III function, potential mechanisms that explain how apoC-III inhibition results in triglyceride reduction in FCS patients include: (1) enhancing the very small residual amounts of LPL activity that these patients may have, below the limit of detection of the assay in many cases (2) potentially enhanced activity of other lipases also involved in the metabolism and breakdown of TGs, such as hepatic lipase or endothelial lipase (Kinnunen and Ehnolm 1976), and (3) apoC-III interaction with Apolipoprotein E (apoE), an important factor in liver reuptake of lipid particles by blocking apoE-mediated uptake of lipid particles in the liver (Breyer et al. 1999), and therefore, reducing apoC-III might enhance apoE-mediated uptake of lipid particles. Volanesorsen-mediated reduction of apoC-III could be contributing to one or all of these mechanisms resulting in the observed potent and sustained reductions in TG.

Through a novel apoC-III lowering mechanism of action, volanesorsen may provide the potential to manage triglyceride levels in FCS patients.

2.3 Volanesorsen

2.3.1 Mechanism of Action

Volanesorsen is a second-generation antisense oligonucleotide (ASO) drug targeted to human apoC-III. It is complementary to a region within the 3′ untranslated region of the apoC-III messenger ribonucleic acid (mRNA) and binds to the mRNA by Watson and Crick base pairing. The hybridization (binding) of volanesorsen to the cognate mRNA, results in the RNase H1-mediated degradation of the apoC-III mRNA, thus preventing production of the apoC-III protein. Maximal antisense-mediated reduction of target mRNA levels is typically greater than 90% of control levels in sensitive tissues (Crooke and Bennett 1996; Zhang et al. 2010). Furthermore, reduction in target mRNA levels using this approach correlates directly with a subsequent reduction in target protein levels.

2.3.2 Chemistry

Chemically, volanesorsen is a synthetic oligomer of 20 nucleotides (i.e., a 20-mer) that are connected sequentially by phosphorothioate linkages. The nucleotide sequence of volanesorsen (Figure 2) is complementary to a 20-nucleotide stretch within the 3′ untranslated region of the apoC-III mRNA transcript at base position 489-508. Structurally, the oligonucleotide has 3 regions. Two (2) of them, the 5 nucleotides at the 5′ end and the 5 nucleotides at the 3′ end, are composed of 2′-*O*-(2-methoxyethyl) (MOE)-modified ribonucleotides. These MOE-modified nucleotides confer (1) increased affinity to the target mRNA (Altmann et al. 1996; McKay et al. 1999), (2) increased resistance to exonucleases and endonucleases (thereby increasing stability in tissue) (Geary et al. 2003), and (3) amelioration of some of the high dose toxicities thereby resulting in an improved safety profile compared to first generation antisense drugs containing phosphorothioate modified oligodeoxynucleotides (DNA) (Henry et al. 2000). The third region, the central portion of the oligonucleotide, is composed of 10 oligodeoxynucleotides. This chimeric design is called a MOE-Gapmer, and volanesorsen employs this chimeric structure to enable use of the RNase H1-mechanism for antisense activity. This is because while the 2′-MOE modification confers increased stability and affinity, it does not support RNase H1 catalysis of RNA hybridized to 2′-MOE-modified nucleotides (McKay et al. 1999). This is caused by conformational changes induced in the heteroduplex by 2′-alkoxy:RNA hybrids that are not recognized by RNase H1 enzymes (Inoue et al. 1987; Monia et al. 1993). By limiting the 2′-MOE modification to nucleotides flanking the phosphorothioate oligodeoxynucleotide core, the beneficial attributes of the 2′-MOE chemistry are preserved while also retaining RNase H1 recognition.

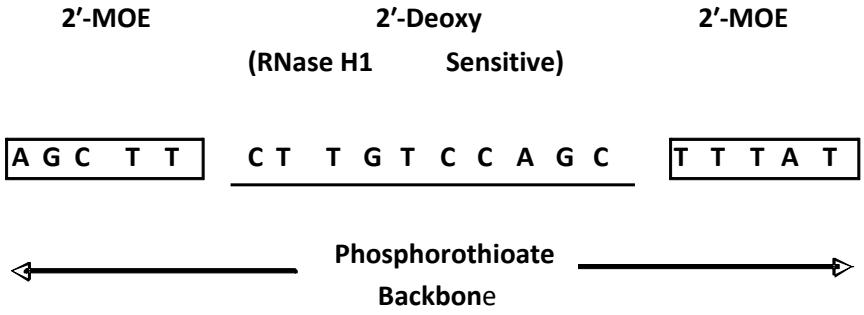


Figure 2 Design of Chimeric 2′-MOE Phosphorothioate Oligonucleotides (MOE-Gapmer). The sequence of volanesorsen is shown

2.3.3 Preclinical Experience

Inhibition of apoC-III using volanesorsen has been shown to potently reduce hepatic apoC-III mRNA as well as plasma apoC-III protein and TG in a dose- and time-dependent fashion in several species, including human apoC-III transgenic mice, and other rodent and monkey models. Treatment with volanesorsen also resulted in reduced VLDL and chylomicron TG and reduced postprandial TG in hypertriglyceridemic monkeys (Graham et al. 2013).

The pharmacokinetics (PK) and toxicity of volanesorsen have been assessed in mice, rats, and cynomolgus monkeys. General toxicity studies with volanesorsen for up to 39 weeks of treatment followed by up to a 20-week recovery period are complete. The preclinical toxicology program for volanesorsen consists of single dose safety pharmacology studies in the monkey (cardiovascular) and

mouse (neurobehavioral and pulmonary assessment studies), *in vitro* and *in vivo* genetic toxicity assessment, repeat dose fertility and/or developmental reproductive toxicology studies in the mouse and rabbit and evaluation in the *in vitro* human Ether-á-go-go-related gene (hERG) assay.

Volanesorsen treatment-related findings in mice and monkeys were generally consistent with those expected for the 2′-MOE-class of ASOs. Treatment-related findings included effects consistent with drug accumulation in tissues in rodents and monkeys, species-dependent proinflammatory response in rodents and monkeys and complement activation and reductions in platelet counts in the monkey. In the mouse and monkey general toxicity studies, reduction of hepatic apoC-III mRNA (> 75%) was not associated with any findings that could be considered related to the pharmacologic inhibition of apoC-III for up to 39 weeks of treatment.

The long-term, chronic toxicology studies in rodents with volanesorsen produced a significant proinflammatory response that led to subsequent effects on the heart at high doses. The rodent species are most sensitive to the proinflammatory effects of antisense molecules. Importantly, these effects on the heart were not observed in the monkey chronic toxicity studies even at the highest doses tested where drug exposure was higher than that in rodents.

Because these changes were not observed in monkeys, the findings in the heart are considered to be rodent-specific and not relevant to humans. Nevertheless, such effects will be monitored by measurement of echocardiograms that will be included in this clinical study.

Volanesorsen caused no untoward effects in safety pharmacology studies (*in vitro* and *in vivo*) and was non-genotoxic (*in vitro* and *in vivo*). Volanesorsen had no effects on fertility or embryo/fetal development in the mouse or rabbit reproductive toxicity studies. In these studies, volanesorsen was detected in placental tissue but not in fetal tissue indicating that little, if any, drug was able to cross the placenta to reach the fetus. Reduction of apoC-III mRNA (64% in males and 47% in females) also did not affect fertility or cause untoward effects on embryo/fetal development in mice.

Detailed information concerning the preclinical studies conducted with volanesorsen can be found in the volanesorsen Investigator's Brochure.

2.3.4 Clinical Experience

Detailed information concerning the clinical studies conducted with volanesorsen can be found in the volanesorsen Investigator's Brochure. A summary is included below.

Volanesorsen has been evaluated in one Phase 1 study and two Phase 2 studies, all double blinded and placebo controlled. The total exposures comprise 99 patients and healthy volunteers administered volanesorsen from 50 to 400 mg subcutaneously up to 3 months (compared to 37 administered placebo).

All clinical trials of volanesorsen have shown large and clinically meaningful reductions in fasting plasma apoC-III and TG (~80% and 70%, respectively, mean reduction from baseline with 300 mg dose) with a very high degree of consistency of response between the different patient groups. This includes healthy volunteers, patients with moderate to severe hypertriglyceridemia not on background TG-lowering therapy, patients with moderate to severe hypertriglyceridemia on a background stable fibrate therapy (Gaudet et al. 2015), patients with FCS, and patients with T2DM.

In a Phase 2 study, 3 patients with FCS were treated with 300 mg/wk volanesorsen in an open-label fashion. These patients had a mean baseline fasting TG level of 1,844 mg/dL and all 3 patients achieved

TG levels below or close to 500 mg/dL during the dosing period out to Day 92 (Figure 3). Two (2) of the FCS patients had an absolute reduction in fasting TG in excess of 1,500 mg/dL (Gaudet et al. 2014).

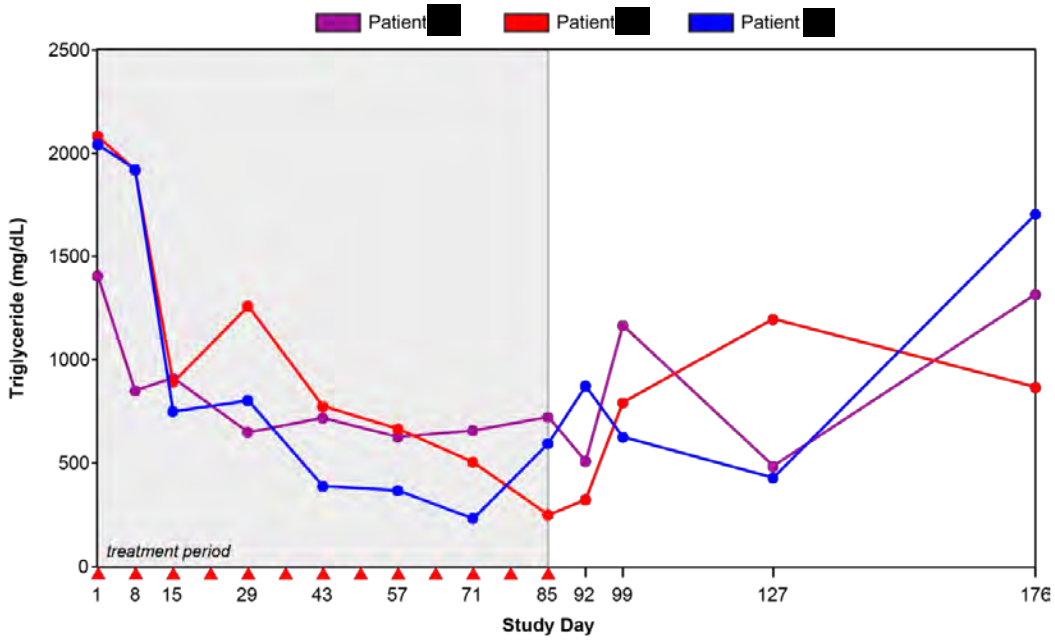


Figure 3 Fasting Triglycerides in Patients with FCS Treated with Volanesorsen

In clinical studies conducted to date volanesorsen has been well-tolerated and has shown a favorable safety profile. There has been no clinical or laboratory evidence of drug-drug interactions.

In the completed studies there have been no volanesorsen associated laboratory abnormalities suggestive of an effect on the renal (serum creatinine, proteinuria) or hepatic systems (alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin). In Phase 2 studies, there was a mild decrease of platelet count associated with volanesorsen administration that recovered in the post-treatment period and was not associated with platelet-related adverse events (AEs). In the blinded ongoing clinical trials of ISIS 304801, 2 patients of 142 dosed (as of February 29, 2016) had a decrease in platelet count to less than 50,000/mm^3 in the absence of major bleeding or clinically-relevant non-major bleeding and had Study Drug paused as per the monitoring and stopping rules for platelet counts (Section 8.6.3). Platelet counts recovered following suspension of dosing.

The most frequently observed AEs with volanesorsen were local reactions at the injection site. Local cutaneous reactions at the injection site defined as those events presenting as either pain, tenderness, erythema, pruritus or swelling occurring on the day of injection and persisting for at least 2 days were infrequent (~15% of injections), were almost always mild, resolved spontaneously, were non-progressive, and were not associated with systemic sequelae.

2.4 Rationale for Dose and Schedule of Administration

The dose and schedule selected for this study is 300 mg per week for 52 weeks, with the option of continuing dosing for an additional 52 weeks. The dose of 300 mg per week is supported by both the cumulative nonclinical data available to date and the Phase 2 clinical data. In nonclinical studies, volanesorsen treatment-related effects in rodents and monkeys were consistent with drug accumulation in

tissues and also include species-specific proinflammatory responses. In the monkey, the No-Observed-Adverse-Effect Level (NOAEL) was defined by the cumulative clinical pathology results and histopathology data which provide an adequate clinical margin. No nonclinical findings were considered to be related to the pharmacologic inhibition of apoC-III.

The safety data to date suggest that volanesorsen has been well-tolerated at dose levels up to 300 mg in patients with high triglycerides (including type 2 diabetes patients and administration in combination with fibrates and statins) with the most common AEs being local to the injection site and predominantly mild. A pooled analysis of safety for the Phase 2 studies did not demonstrate any clear difference in safety or tolerability between the different doses tested (100 mg, 200 mg, and 300 mg per week for 13 weeks).

Analysis of the cohorts in which volanesorsen was studied at different doses demonstrates dose-dependent pharmacology with respect to pharmacodynamic (PD) effect on the target, apoC-III, with a clear difference in the TG-lowering effect between the different doses in the 100 mg to 300 mg dose range as compared to placebo.

In addition to the nonclinical and clinical experience of volanesorsen, the dose and schedule of administration is supported by the preclinical and clinical safety experience of several other 2′-MOE-modified ASOs that have been safely administered intravenously and subcutaneously in multiple clinical studies at doses up to 1000 mg and for treatment durations that exceed 24 months (Santos et al. 2015).

3. EXPERIMENTAL PLAN

3.1 Study Design

This is an open-label study of:

Group 1: ISIS 304801-CS6 (index study) roll over FCS patients

Group 2: ISIS 304801-CS16 (index study) roll over FCS patients

Up to approximately 70 patients will receive 300 mg once weekly volanesorsen for 52 weeks.

Following the Week 52 visit, patients will have the option to continue dosing for up to an additional 52 weeks for a total of 104 weeks of dosing. Patients not to continuing dosing will enter a 26-week post-treatment follow-up period.

3.2 Number of Study Centers

This study will be conducted at multiple centers worldwide.

3.3 Number of Patients

Up to approximately 70 patients will be dosed.

3.4 Overall Study Duration and Follow-up

The Study will consist of the following periods:

3.4.1 Qualification

A qualification period of up to 2 weeks (unless approved by the Sponsor) is given to complete qualification assessments outlined in the Schedule of Procedures. Please refer to Section 4.1 and Appendix A.

3.4.2 Treatment

The treatment period is 52 weeks. Eligible patients will report to the Study Center for assessments at specified intervals throughout the 52-week treatment period as detailed in the Schedule of Procedures (Appendix A). During the treatment period, volanesorsen is administered by SC injection once weekly.

3.4.3 Extended Treatment Period

After completion of the Week 52 visit assessments, patients will have the option of continuing dosing for up to an additional 52 weeks. Patients not continuing dosing will enter the 26-week post-treatment follow-up.

3.4.4 Post-Treatment Follow-Up

The post-treatment follow-up period is at least 26 weeks and consists of at least 9 Study Center visits on Weeks 53, 54, 55, 56, 57, 58, 65, 71, and 78 (Weeks 53, 54, 55, 56, 57, 58, and 71 may be conducted by a home healthcare nurse).

3.5 End-of-Study

The End-of-Study is last patient, last visit.

3.6 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will review (as needed) safety, tolerability and efficacy data collected on volanesorsen during this study. Based on its ongoing assessment of the safety and tolerability of volanesorsen, the DSMB will provide recommendations to the Sponsor for modifying, stopping or continuing the study as planned. Details on the safety assessments, frequency of review and meeting schedules are outlined in the DSMB Charter and/or the statistical analysis plan (SAP).

4. PATIENT ENROLLMENT

4.1 Qualification

Before patients may be enrolled into the study, the Sponsor requires a copy of the Study Center's written independent ethics committee/institutional review board (IEC/IRB) approval of the protocol, informed consent form, and all other patient information.

Patients or their legally acceptable representatives must sign the consent form before any study-specific procedures or evaluations related to this open-label study are performed.

During the qualification period, the eligibility of the patient to enroll in the open-label study will be determined. Final assessments from the ISIS 304801-CS6 or ISIS 304801-CS16 studies may be used for qualification. A period of up to 2 weeks after completion of the ISIS 304801-CS6 or ISIS 304801-CS16 index studies (unless approved by the Sponsor) is given to complete qualification. Qualified patients will retain the unique patient identification number that was assigned to them during the ISIS 304801-CS6 or ISIS 304801-CS16 index studies. The patient identification number will be used to identify the patient throughout the extension trial and must be used on all study documentation related to that patient. The patient identification number must remain constant throughout the extension trial.

4.2 Enrollment

Patients will be enrolled into the treatment phase of the study after all qualification assessments have been completed and after the Investigator has verified that they are eligible per criteria in Sections 5.1 and 5.2. No patient may begin treatment prior to enrollment.

Eligible patients will be enrolled using an Interactive Voice/Web-Response System (IXRS).

5. PATIENT ELIGIBILITY

To be eligible to participate in this study candidates must meet the following eligibility criteria within 2 weeks of Study Day 1, or at the time point specified in the individual eligibility criterion listed.

5.1 Inclusion Criteria

1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law
2. Age ≥ 18 years at time of informed consent
3. Groups 1 and 2: Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement.

   Group 2: Patients who enrolled in ISIS 304801-CS16 must also meet the following criteria in order to enter into the open-label Study:

   a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L)

   b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) supported by documentation of at least 1 of the following:

      - Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1)
      - Post heparin plasma LPL activity of ≤ 20% of normal in medical history. Note: testing of LPL activity should not be performed to confirm eligibility for the study.

   c. Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 index study
4. Able and willing to participate in a 78-week study
5. Satisfy 1 of the following:

   a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved), abstinent*, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration.

b. Males: Surgically sterile, abstinent* or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration.

* Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception

5.2 Exclusion Criteria

1. Diabetes mellitus with any of the following:
   a. Newly diagnosed within 12 weeks of Qualification
   b. HbA1c ≥ 9.0% at Qualification
   c. Recent change in anti-diabetic pharmacotherapy (change in dosage or addition of new medication within 12 weeks of Qualification [with the exception of ± 10 units of insulin])
   d. Anticipated need to change dose or type of medication during the treatment period of the Study (with the exception of ± 10 units of insulin)
   e. Current use of GLP-1 agonists
2. Severe hypertriglyceridemia other than due to familial chylomicronemia syndrome
3. Active pancreatitis within 4 weeks prior to Qualification
4. History within 6 months of Qualification of acute or unstable cardiac ischemia (myocardial infarction, acute coronary syndrome, new onset angina), stroke, transient ischemic attack or unstable congestive cardiac failure requiring a change in medication or major surgery within 3 months of Qualification
5. Any of the following laboratory values at Qualification
   a. Hepatic:
      - Total bilirubin > upper limit of normal (ULN), unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL
      - ALT > 2.0 x ULN
      - AST > 2.0 x ULN
   b. Renal:
      - Persistently positive (2 out of 3 consecutive tests ≥ 1+) for protein on urine dipstick. In the event of a positive test eligibility may be confirmed by a quantitative total urine protein measurement of < 500 mg/24 hrs
      - Persistently positive (2 out of 3 consecutive tests ≥ trace positive) for blood on urine dipstick. In the event of a positive test eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field

- Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault < 50 mL/min (MDRD or CKD-EPI formulas can be used instead of Cockcroft-Gault for estimation of GFR in patients with low body weight after discussion with Sponsor Medical Monitor)

c. Cardiac Troponin I > ULN at Qualification

d. LDL-C > 130 mg/dL at Qualification

e. Any other laboratory abnormalities which, in the opinion of the Investigator or the Sponsor, would make the patient unsuitable for inclusion

6. Uncontrolled hypertension (BP > 160/100 mm Hg)
7. History of thrombocytopenia (platelet count < 100,000/mm^3) or bleeding diathesis or coagulopathy or clinically-significant abnormality in coagulation parameters at Qualification
8. History of heart failure with NYHA greater than Class II
9. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1
10. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B
11. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated
12. Treatment with another investigational drug, biological agent, or device within 1 month of Qualification, or 5 half-lives of investigational agent, whichever is longer
13. Unwilling to comply with lifestyle requirements (Section 6.3)
14. Use of any of the following:

    a. Statins, omega-3 fatty acids (prescription and OTC), or fibrates unless on a stable dose for at least 3 months prior to Qualification and dose and regimen expected to remain constant during the treatment period. Patients taking OTC omega-3 fatty acids should make every effort to remain on the same brand throughout the study

    b. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to Qualification

    c. Systemic corticosteroids or anabolic steroids within 6 weeks prior to Qualification unless approved by the Sponsor Medical Monitor

    d. Atypical antipsychotic medications (e.g., olanzapine and clozapine) unless on a stable dose for at least 3 months prior to Qualification and dose and regimen expected to remain stable throughout the study

    e. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to Qualification and dose and regimen expected to remain constant during the treatment period

    f. Glybera gene therapy within 2 years prior to Qualification

    g. Oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, and apixaban) unless on a stable dose for at least 4 weeks prior to Qualification and regular clinical monitoring is performed

h. Tamoxifen, estrogens or progestins unless on a stable dose for at least 4 months prior to Qualification and dose and regimen expected to remain constant during the treatment period

i. Plasma apheresis within 4 weeks prior to Qualification or planned during the study

j. Prior exposure to ISIS 304801

k. Any other medication unless stable at least 4 weeks prior to Qualification (Occasional or intermittent use of over-the-counter medications will be allowed at Investigator's discretion)

15. Blood donation of 50 to 499 mL within 30 days of Qualification or of > 499 mL within 60 days of Qualification
16. Known hypersensitivity to any of the excipients of the Study Drug (ISIS 304801 or placebo)
17. Have any other conditions, including new or worsening of existing condition, which, in the opinion of the Investigator or the Sponsor would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the study

6. STUDY PROCEDURES

6.1 Study Schedule

All required study procedures are outlined in Appendices A, B, C, and D.

6.1.1 Qualification

Please refer to Section 4.1 and Appendix A.

6.1.2 Treatment Period

The patients, Investigators, study staff, and the Sponsor will remain blinded to lipid data through the last patient's Week 13 visit of the open-label study or until results from the database locks for the ISIS 304801-CS6 and ISIS 304801-CS16 index studies become available, whichever comes first.

During the treatment period, patients will report to the study center for clinic visits a minimum of 5 times during Weeks 1-52 (see Schedule of Procedures in Appendix A). Study Drug will be administered once weekly (Section 8.1). Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), AEs, concomitant medication/procedure information, lipid panel, blood viscosity, volanesorsen plasma concentrations, immunogenicity (IM) testing, platelet aggregation, liver/spleen MRI, ECGs, echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Adverse events at the injection site should be collected as adverse events. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period and all patients will complete a daily food diary for one week prior to their quarterly visit. All blood and urine samples should be collected prior to volanesorsen administration. Blood sampling at Weeks 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, and 51 may be conducted by a home healthcare nurse. Approval for study procedures to be conducted by a home healthcare nurse on other outpatient visit days will require prior approval by the Sponsor. Patients must be fasted prior to drawing all blood samples and samples drawn locally should also be sent to the central laboratory for analysis whenever possible. Dosing instructions and training will be provided to the patient where applicable.

All reasonable attempts should be made to ensure compliance with the visit schedule as outlined in Appendix A. However, in the event that a visit does not occur or is delayed, all subsequent visits should be calculated based on the time elapsed since Day 1 rather than from the date of the previous visit.

6.1.3 Extended Treatment Period

After completion of the Week 52 visit assessments, patients will have the option of continuing dosing for up to an additional 52 weeks.

During the extended treatment period, patients will have assessments and procedures done during Weeks 54-104 as per the Schedule of Procedures in Appendix A. Assessments and procedures may be conducted by either a home healthcare service or the Study Center, however the patient will be required to visit the study center approximately every 3 months. Study Drug will be administered once weekly unless the patient is on a biweekly dosing schedule for safety reasons (Section 8.1). Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), AEs, concomitant medication/procedure information, lipid panel, volanesorsen plasma concentrations, IM testing, ECGs, and physical examinations will be performed according to the Schedule of Procedures in Appendix A. Adverse events at the injection site should be collected as adverse events. Dietary counseling will be reinforced at intervals throughout the extended treatment period. All blood and urine samples should be collected prior to volanesorsen administration. Blood sampling at Weeks 53, 54, 55, 56, 57, 58, 59, 60, 61, 62,63, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, and 103 may be conducted by a home healthcare nurse. Approval for study procedures to be conducted by a home healthcare nurse on other outpatient visit days will require prior approval by the Sponsor. Patients must be fasted prior to drawing all blood samples and samples drawn locally should also be sent to the central laboratory for analysis whenever possible. Dosing instructions and training will be provided to the patient where applicable.

6.1.4 Pharmacokinetic (PK) Subgroup

A subgroup of patients will participate in an extended PK collection. Patients in this subgroup will have more frequent PK sampling over a 24-hour period following the first dose on Study Day 1 in order to evaluate the plasma PK parameters of volanesorsen. Patients in this subgroup will have an additional visit to the clinic, or by a home healthcare nurse, on Day 2 to collect a 24-hour post-dose blood draw after dosing on Day 1. The detailed PK sampling schedules are outlined in Appendix C.

Participation in the PK subgroup is optional for sites and patients, and consent may be withdrawn for the subgroup-specific procedures (e.g., multiple blood draws for PK) without being withdrawn from the study. If a patient withdraws consent from the subgroup procedures, he/she should remain on study and continue to follow all the non-subgroup assessments and procedures as outlined in Appendix A.

6.1.5 Post-Treatment Follow-up

After completion of the Week 52 visit assessments, patients will have the option of continuing dosing for up to an additional 52 weeks as described in Section 6.1.3. Patients not continuing dosing will enter the 26-week post-treatment follow-up. The 26-week post-treatment follow-up consists of at least 9 Study Center visits on Weeks 53, 54, 55, 56, 57, 58, 65, 71, and 78 (Weeks 53, 54, 55, 56, 57, 58, and 71 may be conducted by a home healthcare nurse). An additional 26-week post-treatment follow-up occurs after the extended treatment period with at least 9 Study Center visits on Weeks 105, 106, 107, 108, 109, 110, 117, 118, and 125 (Weeks 105, 106, 107, 108, 109, 110, and 118 may be conducted by a home healthcare nurse. These visits are outlined in the Schedule of Procedures in Appendix A.

6.2 Additional Study Assessments

6.2.1 Laboratory Assessments

Laboratory analyte samples will be collected throughout the study. A list of these analytes is contained in Appendix B.

Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1 week and the result must be reviewed by the Investigator and confirmed to be acceptable before dosing can continue. All platelet count results will be promptly reviewed by the Investigator to determine if the count has met a stopping rule, or the dose reduction rule of 100,000/mm^3, or the dose pause rule of 75,000/mm^3.

Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor.

6.2.2 Physical Exams and Vital Signs

Physical exams and vital signs will be performed as indicated in the Schedule of Procedures (Appendix A). Vital signs should include weight, blood pressure, pulse rate, respiratory rate and body temperature. Blood pressure and pulse rate will be recorded after the patient has been in a sitting position for at least 5 minutes. Semi-supine systolic and diastolic blood pressure should always be measured on the same arm (preferentially on the left arm). Height will be measured at the Day 1 visit.

6.2.2.1 Eruptive Xanthoma

At each visit, patients will be asked whether they have had any episodes of eruptive xanthoma since their last visit and the number/duration of the events will be recorded. Physical exams should also include skin examination for presence/resolution of eruptive xanthomas. If a patient experiences an episode of eruptive xanthoma during the study, photos of the area should be taken, if possible.

6.2.2.2 Lipemia Retinalis

If possible, lipemia retinalis will be assessed by fundus photography prior to administration of the first dose of Study Drug (for ISIS 304801-CS16 roll over patients) and repeated at Week 52. Images will be evaluated by an independent assessor, blinded to the patient's treatment assignment.

6.2.3 Echocardiography

Echocardiography for assessment of left and right ventricular function and mitral and aortic valve function will be conducted at Week 26 and Week 52 in all patients. For the purpose of assessment of treatment-emergent changes, all echocardiograms will be evaluated on an ongoing basis by an independent central reader. Results will be provided to the DSMB for their review.

6.2.4 ECG

The ECG will be recorded after the patient has been resting in a supine position for at least 5 minutes. ECGs will be performed in triplicate at Week 13, Week 26, Week 38, Week 52. During the post-treatment follow-up, ECGs will be performed in triplicate at Weeks 65 and 78 for patients not opting to participate in the Extended Treatment Period. Patients in the Extended Treatment Period will have ECGs performed in triplicate at Weeks 76, 104 and 130.

6.2.5 MRI

MRI of the liver and spleen will be conducted at Week 52 for all patients for whom MRI is not contraindicated, e.g., patients having metal implants.

MRIs will be conducted using standardized procedures and settings. MRIs will be read by an independent central reader to assess liver fat and liver and spleen size**.**

6.2.6 Quality of Life Assessments

All patients will complete Quality of Life Questionnaires (EQ-5D and SF-36) at Week 1, Week 13, Week 26, and Week 52. During the post-treatment follow-up, patients will complete an EQ-5D and SF-36 during Weeks 65 and 78. Additional Quality of Life Questionnaires will be collected at Weeks 117 and 130 should the patient enter the extended treatment period post-treatment follow-up.

6.2.7 Disease Symptom Diary

All patients will complete a symptom questionnaire once a week starting at the beginning of the qualification period and continuing to the end of the post-treatment follow-up period.

6.2.8 Diet Monitoring

The diets of patients enrolled in the study will be monitored as follows:

1. All patients will be required to maintain a 7-day food diary prior to Week 1, Week 13, Week 26, Week 52. During the post-treatment follow-up, patients will complete a 7-day food diary prior to Weeks 65 and 78.
2. Patients will receive diet/alcohol counseling by qualified study personnel at clinic visits throughout the course of the study. Qualified study personnel will telephone the patient to provide diet/alcohol counseling for visits that are conducted by a clinical service.
3. In addition to the 7-day food diary and the diet /alcohol counseling during clinic visits, telephone calls from a dietitian or qualified study personnel to assess as to how each patient is maintaining their diet will be conducted randomly during the treatment and post treatment follow-up periods.

6.2.9 Family History

Family history of hypertriglyceridemia and pancreatitis will be collected for each patient.

6.2.10 Chart Review for Incidents of Acute Pancreatitis in Medical History (Group 2)

Patient records will be reviewed for incidents of acute pancreatitis occurring up to 5 years prior to screening and information relating to these events will be collected for independent adjudication.

6.3 Restriction on the Lifestyle of Patients

6.3.1 Contraception Requirements

All male patients and women of childbearing potential must refrain from sperm/egg donation and either be abstinent or, if engaged in sexual relations of child-bearing potential, practice effective contraception from the time of signing the informed consent form until at least 13 weeks after their last dose of study treatment.

Male patients must also encourage their female partner to use effective contraception from the time of signing the informed consent until 13 weeks after the subject's last dose of study treatment.

For the purposes of this Study, women of childbearing potential are defined as any female who has experienced menarche, and who does not meet 1 of the following conditions:

- Postmenopausal: 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved
- 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Post hysterectomy

For the purposes of the study, effective contraception is defined as follows:

For male patients:

- Effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the use of condoms together with spermicidal foam/gel/film/ cream/suppository. Male patients must also encourage their female partner to use effective contraception from the time of signing the informed consent until 3 months after the patient's last dose of study treatment. Effective contraceptive for the female partner includes: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or barrier methods (female condom*, diaphragm, sponge, cervical cap) together with spermicidal foam/gel/film/cream/suppository. Male patients with partners that are pregnant must use condoms to ensure that the fetus is not exposed to the Study Drug.

For female patients:

- Using 1 or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or any 2 barrier methods (a combination of male or female condom* with diaphragm, sponge, or cervical cap) together with spermicidal foam/gel/film/cream/suppository.

* Note: A female condom and a male condom should not be used together as friction between the two can result in either product failing.

† Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception

6.3.2 Other Requirements

All patients will be required to fast for at least 10 hours and preferably not more than 12 hours before visits requiring fasted blood sampling.

All patients will be encouraged to follow a diet comprising ≤ 20 g fat per day during the study.

Alcohol should not be consumed during the study.

All patients will be given an instruction card that must be presented to the treating physician if a suspected case of pancreatitis occurs. The card will explain that the patient is in a clinical trial and that

serum lipase and/or amylase measures should be done in order to adjudicate the event, based on Atlanta Classification (Banks et al. 2013). If serum or amylase activity is less than 3 x upper limit of normal (ULN), imaging, preferably contrast-enhanced computed tomography, should be considered to confirm the diagnosis of acute pancreatitis per the Atlanta Criteria.

7. STUDY DRUG

7.1 Volanesorsen Description

Volanesorsen drug product (ISIS 304801) characteristics are listed in Table 1.

Volanesorsen (ISIS 304801) is contained in glass prefilled syringes (PFS). Volanesorsen and its storage and preparation instructions will be provided by the Sponsor or designee. Volanesorsen must be stored securely at 2 °C to 8 °C and be protected from light.

Table 1 Volanesorsen (ISIS 304801) Characteristics

Strength	200 mg/mL
Volume/Formulation	1.5 mL solution per PFS
Dose	300 mg once weekly
Route of Administration	SC

7.2 Packaging and Labeling

The Sponsor will provide the Investigator with packaged volanesorsen labeled (ISIS 304801) in accordance with specific country regulatory requirements.

7.3 Study Drug Accountability

The study staff is required to document the receipt, dispensing, and return/destruction of volanesorsen provided by the Sponsor. The Study Center must return all unused volanesorsen to the Sponsor or designee. All used syringes must be disposed of as per the site's hazardous waste destruction policy.

8. TREATMENT OF PATIENTS

8.1 Volanesorsen Administration

For each individual patient, volanesorsen will be administered subcutaneously as a single 1.5 mL 300 mg injection once weekly for Weeks 1-52. Patients entering this ISIS 304801-CS7 study on a reduced dose or dose frequency of Study Drug (volanesorsen), for safety or tolerability reasons in their index study (ISIS 304801-CS6 or ISIS 304801-CS16), will receive a reduced dose or dose frequency of volanesorsen for continued safety or tolerability as outlined in Sections 8.5 and 8.6. Patients entering this CS7 study having dose or dose frequency reduced in the CS16 index study after 13 weeks of treatment, as outlined in CS16 Amendment 4 Section 8.7, can receive the 300 mg once weekly dose of volanesorsen.

Patients should receive 1 dose per week, with weeks always defined relative to Study Day 1. For example, if a patient receives the first dose on a Monday, subsequent doses should be given on Mondays, if possible. If a patient misses an injection, or if dosing on the usual day is not possible, the patient can reschedule the injection provided that 2 doses are administered at least 2 days apart.

Please refer to the Study Drug Manual provided by the Sponsor for more detailed instructions for volanesorsen preparation and administration.

8.2 Other Protocol-Required Drugs

There are no other protocol-required drugs.

8.3 Other Protocol-Required Treatment Procedures

There are no other protocol required treatment procedures for this study.

8.4 Treatment Precautions

There are no specific treatment precautions required for this study.

8.5 Safety Monitoring Rules

Please refer also to the 'Guidance for Investigator' section of the Investigator's Brochure.

For the purposes of safety monitoring baseline is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 (e.g., qualification assessments or assessments from the final visits of ISIS 304801-CS6 and ISIS 304801-CS16 index studies if used for qualification).

In addition to the standard monitoring of clinical safety parameters, the following guidelines are provided for the monitoring of selected parameters chosen based on preclinical and clinical observations.

Confirmation Guidance: At any time during the study (Treatment or Post-Treatment Periods), the initial clinical laboratory results meeting the safety monitoring or stopping criteria presented below **must be confirmed** by performing measurements (ideally in the same laboratory that performed the initial measurement) on new specimens. All new specimen collections should take place as soon as possible (ideally within 3 days of the initial collection). For stopping rules, if the initial laboratory result is observed during the Treatment Period, the results from the retest **must be available** prior to administering the next dose of volanesorsen.

In addition to the safety monitoring parameters listed below, the Sponsor may request confirmation of additional lab values.

Re-dosing Guidance: Patients with initial laboratory test values that reach a stopping rule must not be re-dosed until the re-test results are available. In general, patients who do not meet the stopping rules based upon retest may continue dosing. However, the Investigator and the Sponsor Medical Monitor (or appropriately qualified designee) should confer as to whether additional close monitoring of the patient is appropriate. Reduction in dose or dose frequency may also be initiated as noted in Section 8.7. If any of the stopping criteria described below (refer to Sections 8.6.1 to 8.6.3) are met, the patient will be dose paused or permanently discontinued (as described in the stopping criterion concerned) from further treatment with volanesorsen and evaluated fully as outlined below and in consultation with the Sponsor Medical Monitor or appropriately qualified designee and will be followed up in accordance with Section 8.8 of the protocol.

8.5.1 Safety Monitoring for Liver Chemistry Tests

The following rules are adapted from the draft guidance for industry, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," issued by the U.S. Department of Health and Human Services, Food

and Drug Administration, July 2009. For a definition of Baseline please refer to guidance in Section 8.5 above.

In the event of an ALT or AST measurement that is > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) at any time during the study (Treatment or Post-Treatment Period), the initial measurement(s) should be confirmed as described above. Additional confirmatory measurements should also be performed if ALT or AST levels increase to 5 x ULN.

Frequency of Repeat Measurements: Patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) should have their liver chemistry tests (ALT, AST, alkaline phosphatase (ALP), international normalized ratio (INR) and total bilirubin) retested at least once-weekly until ALT and AST levels become ≤ 1.2 x ULN or 1.2 x baseline value if the baseline value was > ULN.

Further Investigation into Liver Chemistry Elevations: For patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), the following evaluations should be performed:

1. Obtain a more detailed history of symptoms and prior and concurrent diseases
2. Obtain further history for concomitant drug use (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
3. Obtain a history for exposure to environmental chemical agents and travel
4. Serology for viral hepatitis (HAV IgM, HBsAg, HCV antibody, CMV IgM, and EBV antibody panel)
5. Serology for autoimmune hepatitis (e.g., antinuclear antibody [ANA])

Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic CT or MRI scans, may be performed at the discretion of the Investigator, in consultation with the Sponsor Medical Monitor. Repetition of the above evaluations should be considered if a patient's ALT and/or AST levels reach 5 x ULN.

8.5.2 Safety Monitoring for Platelet Count Results

Actions to be taken in the event of reduced platelet count are shown in Table 3 in Section 8.6.3.

Monitor every 1 week unless otherwise specified.

Study Drug administration is contingent on the availability of the immediately preceding test result. An interpretable platelet value must be available within 7 days prior to dosing. Only the study doctor or qualified designee can authorize continued Study Drug administration based on an acceptable platelet value. Patients should not administer a dose until they have been contacted by their study doctor or designee and told that it is acceptable to dose. Authorization to dose must be documented in the patient's medical records.

Due to the 1 to 2-year study duration it is anticipated that patients may undertake travel including vacations, which may impede weekly platelet monitoring. In some situations, it may be possible to arrange for local laboratory testing or use of the home healthcare service at their temporary location. The intent is to maintain weekly platelet monitoring and dosing where possible, as well as Investigator site contact with the study patients. However, if the above options are not possible, a temporary interruption

of study treatment will be planned with a prompt blood draw upon the patient's return which must be reported and reviewed by the Investigator prior to the patient resuming dosing.

The tests outlined in Table 2 should also be performed as soon as possible. Additional lab tests will be determined by the Sponsor Medical Monitor or designee in consultation with the Investigator.

Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor (See also Stopping Rules Section 8.6.3).

Table 2 Labs to Be Performed in the Event of a Platelet Count Less than the Lower Limit of Normal (x2) or < 100,000/mm^3 (x1)*

*In patients who have any 2 occurrences (consecutive or non-consecutive) of platelet count less than the lower limit of normal or who have any 1 occurrence of platelets < 100,000/mm^3. Labs only need to be performed once. Labs may be collected over multiple visits, if blood requirements are a concern, as per investigator discretion.

Note: The following labs may change as additional data is assessed, and sites will be updated regarding any changes.

To Be Performed at Local Lab
Peripheral smear (should be performed locally, fixed and sent to central lab for review)
Fibrinogen split products or D-dimer on fresh blood
To Be Performed at Central Lab
Citrated sample for platelets
Coagulation panel (PT/INR, aPTT)
CBC with reticulocytes
Folate (folic acid)
Vitamin B12
Fibrinogen
von Willebrand factor
Total globulins, total IgA, IgG and IgM
Complement: total C3, total C4, Bb, C5a
hsCRP
Helicobacter pylori (breath test)
Serology for:
HBV, HCV, HIV (if not done recently for screening)
Rubella
CMV
EBV
Parvo B19
Auto-antibody screen:
Antiphospholipid
Rheumatoid factor
Anti-dsDNA
Anti-thyroid
To Be Performed at Specialty Lab(s)
Antiplatelet antibodies and Anti-PF4 assay
Anti-ASO antibody

8.5.3 Safety Monitoring for Minor Bleeding Events

Minor bleeding events are those that do not fulfill the criteria for major bleeding or clinically-relevant, non-major bleeding events (which are defined in Section 8.6.3), for example excess bruising, petechiae, gingival bleeding on brushing teeth. If a minor bleeding event occurs, the Investigator must notify the Sponsor Medical Monitor and additional testing of coagulation parameters activated partial thromboplastin time (aPTT), prothrombin time (PT), INR and platelet count should be performed.

8.5.4 Safety Monitoring for Constitutional Symptoms

Patients will be instructed to promptly report any signs of symptoms of fever or constitutional symptoms that may arise during the study and the Investigator should closely evaluate all potential causes, including concomitant illness. Patients that experience persistent constitutional symptoms should be discussed with the Sponsor Medical Monitor or designee to determine whether additional monitoring or laboratory tests are required.

8.5.5 Safety Monitoring for LDL-C Elevations

Beginning at Week 13, laboratory alerts will be in place to notify the Investigator if a patient has a low-density lipoprotein-cholesterol (LDL-C) > 160 mg/dL (> 130 mg/dL for patients with T2DM) on 2 consecutive visits. If this occurs, LDL-C values for this patient will be unblinded for the remainder of the study and the Investigator will be encouraged to initiate/adjust treatment to lower LDL-C according to country-specific guidelines (e.g., initiate statin therapy or increase the statin dose for patients who are already on treatment).

8.5.6 Safety Monitoring for Insulin, Oral Antidiabetic Medication and Glucose

All patients on insulin will monitor their glucose levels with a glucometer as per standard practice guidelines and bring their glucometer or glucometer log printout to every clinic visit. In addition, patients who are not on insulin but use a glucometer should also bring their glucometer and/or glucometer log printout to every clinic visit.

- The Investigator or delegate will review the glucometer reading or printout at every clinic visit to evaluate if fasting pre-breakfast self-monitored plasma glucose values exceed threshold values as per the Safety Monitoring Rules for Hyperglycemia below.

All diabetic patients will note any changes in their insulin dose and /or oral antidiabetic therapy, as well as any hypoglycemic episode they may experience.

- The Investigator or delegate will ask patients at every clinic visit if they made changes in their insulin dose or oral antidiabetic therapy, and if they experienced a hypoglycemic episode.
    - Patients will be instructed on the monitoring and management of hypoglycemic episodes at each visit.
    - Documented symptomatic hypoglycemic episodes should be captured as adverse events in the adverse event CRF. Documented symptomatic hypoglycemia is defined as typical hypoglycemia symptoms accompanied by measured plasma glucose ≤ 70 mg/dL (≤ 3.9 mmol/L).
    - Any changes in insulin dose or oral antidiabetic therapy should be captured into the Concomitant Medication CRF.

8.5.7 Safety Monitoring for Documented Severe Hypoglycemia

A **documented severe hypoglycemic event** is defined as one in which the patient requires assistance of another person to obtain treatment for the event and has a plasma glucose level ≤ 70 mg/dL (≤ 3.9 mmol/L). The rescue treatment of hypoglycemia may include IV glucose or buccal or intramuscular glucagon.

The definition of severe symptomatic hypoglycemia includes all episodes in which neurological impairment was severe enough to prevent self-treatment and which were thus thought to place patients at risk for injury to themselves or others. Note that "requires assistance" means that the patient could not help himself or herself. Someone being kind that assists spontaneously the patient when not necessary does not qualify as "requires assistance."

Severe hypoglycemia will be qualified as a SAE only if it fulfills SAE criteria.

If a patient presents with symptoms of hypoglycemia, the Investigator will need to take immediate action to confirm the patient's glucose level and treat the patient accordingly.

The experience of hypoglycemia may vary greatly from patient to patient. However, there are certain classical signs and symptoms, of which patients should be aware as a clue that their blood glucose may be low. Common symptoms include headache, heart pounding, confusion, disorientation, numbness or tingling, pale skin, shakiness or tremulousness, increased appetite, anxiousness or nervousness, lightheadedness or dizziness, sweating, and weakness. Coma could occur if blood sugar correction is not performed.

If patients suspect they might be having a hypoglycemia reaction, they should check their blood glucose using their meters as soon as possible, before treatment if possible, provided they feel it is safe to do so. If there is doubt about safety they should treat the event first, using some sugar, milk, or juice for example, then obtain and record a blood glucose value as soon as possible thereafter. The time and nature of treatment should be noted, and especially if any blood glucose result was before or after treatment. It would be helpful for the patient to note if a contributory factor (e.g., missed or reduced meals, unaccustomed physical activity) occurred earlier in the day of the event.

8.5.8 Safety Monitoring for Hyperglycemia

Upward dose titration and/or addition of any other anti-hyperglycemic agent(s) will not be allowed during the course of the study, unless specific threshold values are met at Week 13 or later and confirmed on subsequent testing (ideally within 1 week of the initial test).

HbA1c is monitored every 3 months throughout the study. In addition, patients on insulin should self-monitor their plasma glucose (SMPG) routinely on a glucometer as per practice guidelines. If a fasting pre-breakfast SMPG value exceeds the specific glycemic limit, the patient should check it again on the following 2 days. If all the fasting pre-breakfast values on 3 consecutive days exceed the specific limit, the patient should contact the Investigator and an unscheduled central laboratory FPG measurement and HbA1c should be performed.

The threshold values are defined as:

- FPG > 270 mg/dL (15.0 mmol/L)
- HbA1c > 9% (for patients with baseline HbA1c < 8% and HbA1c increase of more than 1% from baseline (for patients with baseline HbA1c ≥ 8 and < 9%)

In case of confirmed FPG/HbA1c above the threshold value, the Investigator should ensure that no reasonable explanation exists for insufficient glucose control and in particular that:

- Plasma glucose was actually measured in the fasting condition (i.e., after at least 10 hours fast)
- Absence of intercurrent disease which may jeopardize glycemic control. In case of an emergency (e.g., surgery, infection), the Investigator can take appropriate measures for glycemic control
- Compliance to treatment is appropriate
- Compliance to diet and lifestyle is appropriate

If any of the above can reasonably explain the insufficient glycemic control, the Investigator should consider the following:

- Investigation and treatment of intercurrent disease (to be reported in adverse event (AE)/concomitant medication parts of the e-CRF)
- Stress on the absolute need to be compliant to treatment
- Organize a specific interview with a Registered Dietician or other qualified nutrition professional and stress on the absolute need to be compliant to diet and lifestyle recommendations

A FPG/HbA1c follow-up assessment should be arranged after appropriate action has been taken. If none from the above-mentioned reasons can be found, or if appropriate action fails to decrease FPG/HbA1c under the threshold values, additional medication may be introduced at the Investigator's discretion and according to local guidelines after discussion with the Sponsor Medical Monitor.

8.5.9 Acute Pancreatitis

If a patient has an episode of acute pancreatitis, dosing with Study Drug should be suspended temporarily until the patient is clinically stable. The suitability of the patient for continued dosing and the need for any modification to treatment schedule (refer to Section 8.7) will be determined by the Investigator in consultation with the Study Medical Monitor.

8.6 Stopping Rules

For the purposes of stopping rules baseline is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1.

8.6.1 Stopping Rules for Liver Chemistry Elevations

In the event of laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor,** dosing of a patient with volanesorsen will be stopped permanently; values that are not confirmed due to failure to retest or missing lab values will be presumed confirmed:

1. ALT or AST > 8 x ULN, which is confirmed
2. ALT or AST > 5 x ULN, which is confirmed and persists for ≥ 2 weeks
3. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed **and** total bilirubin > 2 x ULN or INR > 1.5

4. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed, and the new appearance (i.e., onset coincides with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> ULN) felt by the Investigator to be potentially related to hepatic inflammation

8.6.2 Stopping Rules for Renal Function Test Results

In the event of a persistent elevation that is observed over 2 consecutive weeks, for any of the 3 criteria below, dosing of a patient with volanesorsen may be stopped temporarily:

1. Serum creatinine increase that fulfill all of the following criteria: ≥ 0.3 mg/dL (26.5 µmol/L) and ≥ 40% above baseline creatinine values and > ULN
2. Proteinuria, dipstick 2 + (confirmed by dipstick retest and then further confirmed by a quantitative total urine protein measurement of > 1.0 g/24 hour)
3. Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault ≤ 40 mL/min that is confirmed by a 24-hour urine collection

The possible dosing re-initiation or follow-up schedule for any events meeting either of these criteria will be determined by the Investigator **in consultation with** the Sponsor Medical Monitor or designee.

8.6.3 Stopping Rules for Platelet Count Results

Actions to be taken in the event of a low platelet count are summarized in Table 3 below.

In the event of a platelet count less than 75,000/mm^3 that is associated with major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with volanesorsen will be stopped permanently. The follow-up schedule for any events meeting this stopping criterion will be determined by the Investigator in consultation with the Sponsor Medical Monitor.

In the event of any platelet count less than 50,000/mm^3, or a rate of decline ≥ 50% between two consecutive assessments, irrespective of the platelet level, or a platelet count less than 75,000/mm^3 that occurs while the patient is on dosing at 300 mg every 2 weeks, then dosing of a patient with volanesorsen will be stopped permanently. Platelet count will be monitored as outlined in Table 3.

Administration of steroids is recommended for patients whose platelet count is less than 50,000/mm^3. Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days
(**note:** may require continuation with oral steroids after methylprednisolone). In order to reduce the unlikely but potential increased risk of pancreatitis during the period of corticosteroid therapy, triglyceride levels will be monitored weekly, and AE monitoring will continue, during corticosteroid treatment and the laboratory alert will be changed from an increase of 2,000 to 500 mg/dL during that period.

In the event of a platelet count less than 75,000/mm^3, and in the absence of major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with volanesorsen should be suspended temporarily until the platelet count has recovered to> 100,000/mm^3. If dosing is continued it should be at a reduced dose frequency of 300 mg every 2 weeks (refer to Section 8.7). The

suitability of the patient for continued dosing will be determined by the Investigator in consultation with the Study Medical Monitor and will be based on factors such as the original rate of decline in the patient's platelet count, whether any bleeding events were experienced by the patient, and the speed of recovery of platelet count upon holding of dosing.

If after the first dosing rechallenge the platelet count again falls below 75,000/mm^3, then dosing of the patient with Study Drug will be stopped permanently.

Definition of Major Bleeding Events (Schulman et al. 2005):

- Fatal bleeding, and/or
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarterial or pericardial, or intramuscular with compartment syndrome, and/or
- Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more within 24 hours, or leading to transfusion of 2 or more units of whole or red cells

Definition of Clinically-Relevant, Non-Major Bleeding Events (Schulman et al. 2005):

1. Multiple-source bleeding
2. Spontaneous hematoma > 25 cm^2
3. Excessive wound hematoma (not injection site related)
4. Macroscopic hematuria (spontaneous or lasting > 24 hours if associated with an intervention)
5. Spontaneous rectal bleeding; epitasis, gingival bleeding, hemoptysis, hematemesis
6. Bleeding after venipuncture for > 5 minutes

Table 3 Actions in Patients with Low Platelet Count

Platelet Count on Rx	Drug Dose	Monitoring
	Study Drug administration is contingent on the availability of the immediately preceding test result. An interpretable platelet value must be available within 7 days prior to dosing. Only the study doctor or qualified designee can authorize continued Study Drug administration based on an acceptable platelet value. Patients should not administer a dose until they have been contacted by their study doctor or designee and told that it is acceptable to dose. Authorization to dose must be documented in the patient's medical records.	Monitor every 1 week unless otherwise specified Obtain additional lab tests (Table 2) if 2 occurrences consecutive or non-consecutive of platelet count 140K - > 100K/mm^3 or 1 occurrence of platelet count ≤ 100K/mm^3. Labs only need to be performed once. Labs may be collected over multiple visits, if blood requirements are a concern, as per Investigator discretion.
> 100K/mm^3	Weekly 300 mg Study Drug administration	
100K/mm^3 - >75K/mm^3	Permanently reduce dose frequency to 300 mg every 2 weeks	

Platelet Count on Rx	Drug Dose	Monitoring
75K/mm^3 - >50K/mm^3	• If occurs while on dose of 300 mg every 2 weeks then permanently discontinue Study Drug, otherwise dose pause. • When platelet count returns to > 100K/mm^3 restart dosing at dose frequency of 300 mg every 2 weeks **only if approved by Sponsor Medical Monitor**	• Monitor every 2-3 days until 2 successive values are > 75K/mm^3 then monitor every 1 week • Consider discontinuation of antiplatelet agents/NSAIDS/ anticoagulant medication
< 50K/mm^3 or a rate of decline ≥ 50% between two consecutive assessments, irrespective of the platelet level	Permanently discontinue Study Drug	• Monitor daily until 2 successive values show improvement then monitor every 2-3 days until 2 successive values are > 75K/mm^3 then monitor every 1 week • Patient should be evaluated by a hematologist to provide diagnostic and therapeutic management • Steroids recommended *. It is strongly recommended that, unless the patient has a medical contraindication to receiving glucocorticoids, the patient receives glucocorticoid therapy to reverse the platelet decline. • Monitor triglyceride levels weekly and continue AE monitoring during steroid therapy • Discontinue antiplatelet agents/ NSAIDS/ anticoagulant medication while platelet count is< 50K/mm^3 if possible

Legend:

* Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (**note**: may require continuation with oral steroids after Methylprednisolone). In order to reduce the unlikely but potential increased risk of pancreatitis during the period of corticosteroid therapy, triglyceride levels will be monitored weekly, and AE monitoring will continue, during corticosteroid treatment and the laboratory alert will be changed from an increase of 2,000 to 500 mg/dL during that period.

8.7 Adjustment of Dose Frequency

Dose adjustments for platelet count reduction must be made in accordance with Section 8.6.3 and Table 3 (above).

Other dose adjustments, including dose interruptions, and/or decreasing the dose or dose frequency will be allowed for safety and tolerability. Any proposed adjustment to treatment schedule must be discussed with, and approved by, the Study Medical Monitor prior to initiation. Up to 2 adjustments in the treatment schedule may be allowed.

Patients may be dose paused in response to AEs after consultation with Study Medical Monitor.

8.8 Discontinuation of Study Treatment

A patient must permanently discontinue study treatment for any of the following:

- The patient becomes pregnant. Report the pregnancy according to instructions in Section 9.5.4
- The patient withdraws consent
- The patient experiences an AE that necessitates permanent discontinuation of study treatment
- The patient develops laboratory test abnormalities that meet any of the stopping rules listed in Section 8.6

The reason for discontinuation of study treatment must be recorded in the CRF and source documentation.

8.8.1 Follow-up Visits for Early Termination from Treatment Period

Any patient who discontinues early from the Treatment Period should be followed as per the platelet monitoring rules shown in Table 3 in Section 8.6.3 for the first 6 weeks after discontinuing Study Drug. Following this period, if the platelet count is stable (at least 3 consecutive values that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3), the next platelet count should be taken within at least 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug. Patients should also be strongly encouraged to attend applicable landmark visits at Weeks 12, 13, 25, 26, and 50, 52 (calculated based on the time elapsed since Day 1) to collect fasting lipid panels and conduct safety assessments in accordance with the Schedule of Procedures in Appendix A. Any patient who discontinues treatment after Week 44 should also be strongly encouraged to attend a final follow-up visit (Week 78 visit assessments) approximately 26 weeks after their last dose of Study Drug, in addition to the applicable landmark visits.

If the patient declines or is unable to participate in the above, an early termination (ET) visit (Week 52 visit assessments) should be performed at the time of withdrawal, at a minimum, and ideally within 2 weeks from the last dose of Study Drug.

8.8.2 Follow-up Visits for Early Termination from Post-Treatment Follow-up Period

The patient who requests to withdraw from the study during the Post-Treatment Follow-up Period should be encouraged to follow the platelet monitoring rules shown in Table 3 in Section 8.6.3 for the first 6 weeks after discontinuing Study Drug. Following this period, if the platelet count is stable (at least 3 consecutive values that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3), the next platelet count should be taken within at least 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug. Patients should also be encouraged to undergo a final follow-up visit (Week 78, see Appendix A) prior to leaving the study.

If a patient withdraws due to an AE at any time during the study, the Investigator should arrange for the patient to have appropriate follow-up until the AE has resolved or stabilized.

8.9 Withdrawal of Patients from the Study

Patients must be withdrawn from the study for any of the following:

- Withdrawal of consent
- The patient is unwilling or unable to comply with the protocol

Other reasons for withdrawal of patients from the study might include:

- At the discretion of the Investigator for medical reasons
- At the discretion of the Investigator or Sponsor for noncompliance
- Significant protocol deviation

All efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information, including the reason for withdrawal from study, must be recorded in the CRF.

Any patient who withdraws consent to participate in the study will be removed from further treatment and study observation immediately upon the date of request. These patients should be encouraged to complete the ET study procedures and observations at the time of withdrawal (see Section 8.8 and Appendix A).

For patients withdrawn for reasons other than withdrawal of consent every effort should be made to complete the early termination study procedures and observations at the time of withdrawal (see Section 8.8 and Appendix A).

8.10 Concomitant Therapy and Procedures

The use of concomitant therapies or procedures defined below must be recorded on the patient's CRF. AEs related to administration of these therapies or procedures must also be documented on the appropriate CRF.

8.10.1 Concomitant Therapy

A concomitant therapy is any non-protocol specified drug or substance (including over-the-counter medications, herbal medications and vitamin supplements) administered between signing informed consent and completion of the post-treatment follow-up period. All concomitant medications/treatments and significant non-drug therapies (including supplements and assistive devices) received by a patient, including changes in the patient's current medications, must be recorded in the patient's source documents and CRF. Patients taking over the counter (OTC) omega-3 fatty acids should make every effort to remain on the same brand throughout the study.

Allowed Concomitant Therapy

Any medications deemed necessary by the Investigator are allowed except those listed in the disallowed concomitant therapy.

Disallowed Concomitant Therapy

No lipid lowering therapies (e.g., fibrates, niacin, fish oil or other products containing omega-3 fatty acids [including OTC preparations]), -glucagon-like peptide-1 (GLP-1) agonists, Glybera, or systemic corticosteroids may be started or adjusted after baseline Qualification. Doses of existing oral anti-diabetic medication, oral contraceptives, hormone replacement therapy, anticoagulants, or drugs or dietary supplements with potential lipid-altering effects should not be adjusted. Study patients are prohibited from receiving other experimental agents during the study. This includes marketed agents at experimental dosages that are being tested for the treatment of hypertriglyceridemia.

Patients should consult with the Site Investigator or designee prior to initiating any new medication, including non-prescription or herbal compounds or any other non-drug therapy.

8.10.2 Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between signing of informed consent and Week 78 visit.

Disallowed Concomitant Procedure

Plasma apheresis is not allowed during the study.

8.11 Treatment Compliance

Compliance with treatment dosing is to be monitored and recorded by Study Center staff. The Study Center staff is required to document the receipt, dispensing, and return/destruction of volanesorsen. Patients that are self-administering volanesorsen at home must record treatment in a dosing diary that will be reviewed periodically by Study Center staff and the Clinical Monitor.

9. SERIOUS AND NON-SERIOUS ADVERSE EVENT REPORTING

9.1 Sponsor Review of Safety Information

Safety information will be collected, reviewed, and evaluated by the Sponsor in accordance with the Safety Management Plan throughout the conduct of the clinical trial.

9.2 Regulatory Requirements

The Sponsor is responsible for regulatory submissions and reporting to the Investigators of serious adverse events (SAEs) including suspected unexpected serious adverse reactions (SUSARs) per the International Conference on Harmonization (ICH) guidelines E2A and ICH E6 (R2). Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines.

Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) will be notified of any SAE according to applicable regulations. The Independent DSMB will be notified of any SAE as specified in the DSMB charter.

In addition to the Investigator's assessment of relatedness, the Sponsor or designee will evaluate the available information and perform an independent assessment of relatedness. While the Sponsor may upgrade an Investigator's decision it is not permissible to downgrade the Investigator's opinion for the purposes of determining whether the SAE meets the definition of a SUSAR.

The following table identifies the SAEs that the Sponsor or designee will not report on an individual basis in an expedited manner because they are anticipated to occur in the study population independent of volanesorsen exposure. The Investigator still has the responsibility to report all SAEs to the Sponsor as described in Sections 9.4.1 to 9.4.3.5.

Table 4 Expected Event for the Protocol Defined Population by Preferred Term and the Expected Incidence

Preferred Term	Expected Incidence in the Protocol Defined Population (Gaudet et al. 2010 and 2013)
Pancreatitis associated events including the PTs of hereditary pancreatitis, pancreatitis, pancreatitis acute, pancreatitis chronic, pancreatitis necrotizing, pancreatitis relapsing	0.2-0.35 events per patient-year

Fatal pancreatitis associated events will be considered as unexpected and are reportable. The Sponsor and DSMB will monitor non-fatal pancreatitis associated SAEs using the incidence rate of the event compared to the rate expected in a non-volanesorsen exposed population. If the aggregate analysis indicates that an event is occurring significantly more frequently or at a greater severity than expected, then the event will be reported.

SAEs not specified in the table will be evaluated on case by case basis to determine whether there is a reasonable possibility that the drug caused the event. If the event is considered by the Sponsor or designee to meet the definition of a SUSAR the event will be reported.

9.3 Definitions

9.3.1 Adverse Event

An adverse event is any unfavorable and unintended sign (including a clinically-significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the study or use of investigational drug product, whether or not the AE is considered related to the investigational drug product.

9.3.2 Adverse Reaction and Suspected Adverse Reaction

An adverse reaction is any adverse event caused by volanesorsen.

A suspected adverse reaction is any adverse event for which there is a reasonable possibility that volanesorsen drug caused the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

9.3.3 Serious Adverse Event (SAE)

A serious adverse event is any adverse event that in the view of either the Investigator or Sponsor, meets any of the following criteria:

- Results in death
- Is life threatening: that is, poses an immediate risk of death at the time of the event

An AE or suspected adverse reaction is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Hospitalization is defined as an admission of greater than 24 hours to a medical facility and does not always qualify as an AE
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- Results in congenital anomaly or birth defect in the offspring of the patient (whether the patient is male or female)
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

9.4 Monitoring and Recording Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the study (i.e., before informed consent) should be recorded as Medical History and not recorded as AEs unless the pre-existing condition worsened. The Investigator should always group signs and symptoms into a single term that constitutes a **single unifying diagnosis** if possible.

9.4.1 Serious Adverse Events

In the interest of patient safety, and in order to fulfill regulatory requirements**,** all SAEs (regardless of their relationship to volanesorsen) should be reported to the Sponsor or designee within 24 hours of the Study Center's first knowledge of the event. The collection of SAEs will begin after the patient signs the informed consent form and stop at the end of the patient's follow-up period which is defined as the Week 78 visit. When the Investigator is reporting by telephone, it is important to speak to someone in person versus leaving a message. An Initial Serious Adverse Event Form should be completed and a copy should be faxed to the Sponsor or designee.

Detailed information should be actively sought and included on Follow-Up Serious Adverse Event Forms as soon as additional information becomes available. All SAEs will be followed until resolution. SAEs that remain ongoing past the patient's last protocol-specified follow-up visit will be evaluated by the Investigator and Sponsor. If the Investigator and Sponsor agree the patient's condition is unlikely to resolve, the Investigator and Sponsor will determine the follow-up requirement.

9.4.2 Non-Serious Adverse Events

The recording of non-serious AEs will begin after the patient signs the informed consent form and will stop at the end of the patient's follow-up period, which is defined as the Week 78 visit. The Investigator will monitor each patient closely and record all observed or volunteered AEs on the Adverse Event Case Report Form.

9.4.3 Evaluation of Adverse Events (Serious and Non-Serious)

The Investigator's opinion of the following should be documented on the Adverse Event Case Report Form:

9.4.3.1 Relationship to the Study Drug

The event's relationship to volanesorsen is characterized by 1 of the following:

- **Related:** There is clear evidence that the event is related to the use of volanesorsen, e.g., confirmation by positive rechallenge test

- **Possible:** The event cannot be explained by the patient's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and volanesorsen administration
- **Unlikely/Remote:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to volanesorsen administration and/or exposure suggests that a causal relationship is unlikely (For reporting purposes, Unlikely/Remote will be grouped together with Not Related)
- **Not Related:** The event can be readily explained by the patient's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and volanesorsen

9.4.3.2 Severity

The severity of AEs and SAEs will be graded based on criteria from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010 (refer to Appendix D). Any AE not listed in Appendix D will be graded as follows:

- **Mild:** The event is easily tolerated by the patient and does not affect the patient's usual daily activities
- **Moderate:** The event causes the patient more discomfort and interrupts the patient's usual daily activities
- **Severe:** The event is incapacitating and causes considerable interference with the patient's usual daily activities

If the event is an SAE, then all applicable seriousness criteria must be indicated (criteria listed in Section 9.3.3).

9.4.3.3 Action Taken with Volanesorsen

Action taken with volanesorsen due to the event is characterized by 1 of the following:

- **None:** No changes were made to volanesorsen administration and dose
- **Permanently Discontinued:** Volanesorsen was discontinued and not restarted
- **Temporarily Interrupted, restarted – same dose:** Dosing was temporarily interrupted or delayed due to the AE and restarted at the same dose
- **Reduced schedule:** Dosing frequency was reduced

9.4.3.4 Treatment Given for Adverse Event

Any treatment (e.g., medications or procedures) given for the AE should be recorded on the Adverse Event Case Report Form (treatment should also be recorded on the concomitant treatment or ancillary procedures CRF as appropriate).

9.4.3.5 Outcome of the Adverse Event

If the event is a non-serious AE then the event's outcome is characterized by 1 of the following:

- **AE Persists:** Patient terminates from the trial and the AE continues

- **Recovered:** Patient recovered completely from the AE
- **Became Serious:** The event became serious (the date that the event became serious should be recorded as the Resolution Date of that AE and the Onset Date of the corresponding SAE)
- **Change in Severity** (if applicable): AE severity changed

If the event is a SAE then the event's outcome is characterized by 1 of the following:

- **Ongoing:** SAE continuing
- **Persists (as non-serious AE):** Patient has not fully recovered but the event no longer meets serious criteria and should be captured as an AE on the non-serious AE eCRF (the SAE resolution date should be entered as the date of onset of that AE)
- **Recovered:** Patient recovered completely from the SAE (the date of recovery should be entered as the SAE resolution date)
- **Fatal:** Patient died (the date of death should be entered as the SAE resolution date)

9.4.4 Adjudication Committees

All SAEs that occur during the study that are consistent with a major acute cardiovascular event (MACE) will be adjudicated by a blinded, independent committee as outlined in the MACE Adjudication Charter.

All AEs and SAEs that occur during the study that are consistent with an event of acute pancreatitis will be adjudicated by a blinded, independent committee according to the Atlanta classification of acute pancreatitis (Banks et al. 2013) and as outlined in the Pancreatitis Adjudication Charter. In addition, data for prior episodes of acute pancreatitis or suspected pancreatitis will be collected by review of each patient's medical chart and these events will also be adjudicated.

9.5 Procedures for Handling Special Situations

9.5.1 Abnormalities of Laboratory Tests

Clinically-significant abnormal laboratory test results may, in the opinion of the Investigator, constitute or be associated with an AE. Examples of these include abnormal laboratory results that are associated with symptoms, or require treatment, e.g., bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac arrhythmias due to hyperkalemia. Whenever possible, the underlying diagnosis should be listed in preference to abnormal laboratory values as AEs. Clinically-significant abnormalities will be monitored by the Investigator until the parameter returns to its baseline value or until agreement is reached between the Investigator and Sponsor Medical Monitor. Laboratory abnormalities deemed not clinically-significant (NCS) by the Investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator should not be deemed NCS on the laboratory sheet.

The Investigator is responsible for reviewing and signing all laboratory reports. The signed clinical laboratory reports will serve as source documents and should include the Investigator's assessment of clinical significance of out of range/abnormal laboratory values.

9.5.2 Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the patient is hospitalized; the Study Center must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the patient's consent to participate in the study
- The condition that required the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the patient's consent to participate in the study and the timing of the procedure or treatment
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission

9.5.3 Dosing Errors

Volanesorsen dosing errors should be documented as Protocol Deviations. A brief description should be provided in the deviation, including whether the patient was symptomatic (list symptoms) or asymptomatic, and the event accidental or intentional.

Dosing details should be captured on the Dosing Case Report Form. If the patient takes a dose of volanesorsen that exceeds protocol specifications and the patient is symptomatic, then the symptom(s) should be documented as an AE and be reported per Section 9.4.

Should an overdose occur, the Investigator or designee should refer to the Guidance to Investigator's section of the Investigator's Brochure and contact the Sponsor or designee within 24 hours.

9.5.4 Contraception and Pregnancy

Male patients and female patients of childbearing potential must continue to use appropriate contraception with their partners, or refrain from sexual activity, as described in Section 6.3.1.

If a patient becomes pregnant or a pregnancy is suspected, or if a male patient makes or believes that he has made someone pregnant during the study, then the Study Center staff must be informed immediately. An Initial Pregnancy Form should be submitted to the Sponsor or designee **within 24 hours** of first learning of the occurrence of pregnancy. Follow-up information including delivery or termination is reported on Follow-up Pregnancy Forms and reported within 24 hours.

Payment for all aspects of obstetrical care, child or related care will be the patient's responsibility.

Female patients: If a suspected pregnancy occurs while on the study (including follow-up), a pregnancy test will be performed. The patient with a confirmed pregnancy will be immediately withdrawn from treatment with volanesorsen. However, the patient will be encouraged to complete the post-treatment follow-up portion of the study to the extent that study procedures do not interfere with the pregnancy. Regardless of continued study participation, the study physician will assist the patient in getting obstetrical care and the progress of the pregnancy will be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the Study Center and Sponsor may require access to the mother and infant's medical records for an additional 8 weeks after birth.

Male patients: The progress of the pregnancy in a male patient's partner should be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, **the Study Center and Sponsor may request access to the**

mother and infant's medical records for an additional 8 weeks after birth. Follow-up will be performed to the extent permitted by applicable regulations and privacy considerations.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints

For fasting lipid measurements, the values at Month 3 analysis time point are defined as the average of Week 12 (Day 78) and Week 13 (Day 85) fasting assessments, the values of Month 6 analysis time point is at the end of Month 6 are defined as the average of Week 25 (Day 169) and Week 26 (Day 176) fasting assessments, and the values at the Month 12 analysis time point are defined as the average of Week 50 (Day 344) and Week 52 (Day 358) fasting assessments.

10.1.1 Efficacy Endpoints

- Percent change and absolute change from baseline in fasting TG
- Frequency and severity of patient reported abdominal pain during the treatment period
- Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-HDL-C, apoB, HDL-C, apolipoprotein A-1 (apoA-1), VLDL-C, and LDL-C
- Percent change from baseline in fasting total apolipoprotein C-III
- Change in blood viscosity (may be evaluated)
- Quality of Life questionnaires (EQ-5D, SF-36)
- Adjudicated acute pancreatitis event rate
- Other symptoms: eruptive xanthoma, lipemia retinalis

10.1.2 Safety Endpoints

- Adverse events including adjudicated events of pancreatitis and MACE
- Vital signs and weight
- Physical examinations
- Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis)
- Echocardiography
- Electrocardiograms (ECGs)
- Use of concomitant medications
- MRIs
- Platelet aggregation (may be evaluated)

10.2 Sample Size

No sample size calculations were performed as this is an open-label study.

10.3 Populations

Full Analysis Set (FAS): All patients who are enrolled and received at least 1 dose of active Study Drug and have a baseline TG assessment. The FAS represents the practically-feasible intent-to-treat (ITT) population as delineated in ICH Guideline E9.

Per Protocol Set (PPS): Subset of the FAS who received 9 of first 13 scheduled doses of volanesorsen and with no significant protocol deviations that would be expected to affect efficacy and PD assessments. The detailed criteria will be specified and finalized prior to the final database lock.

Safety Set: All patients who are enrolled and receive at least 1 dose of volanesorsen.

PK Population: All patients who are enrolled, receive at least 1 dose of volanesorsen, and have at least 1 post first dose PK sample collected, analyzed, and reported.

10.4 Definition of Baseline

Definitions of baseline are given below for the purposes of the final analysis.

For fasting lipid measurements, 2 baselines are defined for each patient in Groups 1 and 2: Group 1 (ISIS 304801-CS6) or Group 2 (ISIS 304801-CS16) index study baseline and the baseline in this open-label study, which is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 (e.g., qualification assessments or assessments from final visit of the ISIS 304801-CS6 or ISIS 304801-CS16 index studies if used for qualification).

For other measurements, baseline for patients on active treatment in the ISIS 304801-CS6 or ISIS 304801-CS16 index study will be the ISIS 304801-CS6 or ISIS 304801-CS16 index study baseline. For patients on placebo in the ISIS 304801-CS6 or ISIS 304801-CS16 index study, baseline will be the last non-missing assessment prior to the first dose of Study Drug. Details will be provided in the SAP.

10.5 Interim Analysis

An interim analysis may be conducted after the last patient's Week 13 visit of the open-label study or after the database of the ISIS 304801-CS6 and ISIS 304801-CS16 index studies are locked and unblinded. Both safety and efficacy information from this open-label study may be summarized during this interim analysis. Efficacy analyses will be detailed in the SAP.

10.6 Planned Methods of Analysis

All eCRF data, lab data transfers, as well as any outcomes derived from the data, will be provided in the patient data listings. Patient data listings will be presented for all patients enrolled into the study. Descriptive summary statistics including n, mean, median, standard deviation, standard error, interquartile range (25th percentile, 75th percentile), and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data by treatment group of the index studies for patients on active Study Drug in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies, and pooled treatment naïve group which includes patients on placebo in index studies. Where appropriate, p-values will be reported. All statistical tests will be conducted using 2-sided tests with 5% Type I error rates unless otherwise stated.

TG related endpoints will be assessed in the FAS and PPS, and all other efficacy endpoints will be assessed in the FAS. All safety assessments will be performed on the Safety Set. PK endpoints will be assessed in the PK Set as applicable.

10.6.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics by treatment group and overall. The patient disposition will be summarized by treatment group and overall. All patients enrolled will be included in a summary of patient disposition.

10.6.2 Safety Analysis

Treatment duration and amount of Study Drug received will be summarized by treatment group and overall.

Patient incidence rates of AEs will be tabulated by MedDRA system organ class, MedDRA preferred term, and treatment group of the index studies. Narratives of treatment-emergent deaths, serious and significant AEs, including early withdrawals due to AEs, will also be provided.

All treatment-emergent AEs, all treatment-emergent AEs potentially related to Study Drug, all treatment-emergent serious AEs, and all treatment-emergent serious AEs potentially related to Study Drug will be summarized.

Injection Site Reactions (ISRs) will be summarized by treatment group, MedDRA preferred term and severity.

Independently adjudicated events of MACE and pancreatitis will be summarized by treatment group.

Laboratory tests to ensure patient safety including chemistry panel, complete blood count (CBC) with differential, coagulation panel, IM, complement etc., will be summarized by study visits by treatment group.

These safety variables will also be presented as change and percent change from baseline over time after Study Drug administration, as appropriate.

Vital signs, weight, ECG measures, echocardiography assessments, and MRI assessments will be tabulated by treatment group.

10.6.3 Efficacy Analysis

Percent change and change from baseline to Month 3, Month 6, and Month 12 in fasting TG will be summarized by treatment group. Response rate of patients with fasting plasma TG < 750 mg/dL or achieving fasting TG $\geq 40\%$ reduction from baseline at Month 3, Month 6, and Month 12 will be summarized. Response analysis will also be conducted using a range of fasting plasma TG thresholds for determination of responder status.

Percent change and change from baseline to Month 3, Month 6, and Month 12 will also be summarized by treatment group for other fasting lipid measures including non-HDL-C, apoB, HDL-C, apoA-1, VLDL-C, and LDL-C, total cholesterol, and fasting total apoC-III.

The incremental effects of volanesorsen on lipid measures will be explored and the association between changes in lipid parameters and total amount of drug received will be examined, as appropriate.

Frequency and severity of patient reported abdominal pain, adjudicated acute pancreatitis event rate, quality of life assessments, and comparison of other symptoms including eruptive xanthomas and lipemia retinalis will be summarized by treatment group.

Additional details of the analyses to be conducted will be provided in the SAP.

10.6.4 Pharmacokinetic and Immunogenicity Analysis

10.6.4.1 Pharmacokinetic Analysis

For all patients, pre-dose and post-treatment volanesorsen plasma concentrations will be summarized using descriptive statistics by treatment group and IM status.

For patients in the PK subgroup only, non-compartmental PK analysis of volanesorsen will be carried out on each individual patient data set using data collected in the open-label study from the intensive PK subgroup, following a single-dose (i.e., single-dose PK) or multiple doses (i.e., steady-state PK), depending on their earlier treatment in the index studies (Group 1 and 2 patients). On Week 1 Day 1 of the open-label study, patients who received placebo in the index study will receive the first treatment of volanesorsen (single-dose PK), while patients who received volanesorsen in the index studies had been on volanesorsen treatment for 12 months (ISIS 304801-CS6) or 6 months (ISIS 304801-CS16), thus the PK data collected from these patients reflect steady-state PK. The maximum observed drug concentration (C_{max}) and the time taken to reach C_{max} (T_{max}) will be obtained directly from the concentration-time data. Area under the plasma concentration-time curve from time zero to 24 hours ($AUC_{0\text{-}24h}$) will be calculated using the linear trapezoidal rule. Apparent systemic (plasma) clearance after SC administration ($CL_{0\text{-}24h}$ /F) will be calculated from $CL_{0\text{-}24h}$ /F = Actual Dose/$AUC_{0\text{-}24h}$. Mean residence time (MRT) from time zero to 24 hours after the SC administration will be calculated from the equation, $MRT_{0\text{-}24h} = AUMC_{0\text{-}24h}$ /$AUC_{0\text{-}24h}$, where $AUMC_{0\text{-}24h}$ is the area under the moment plasma concentration-time curve from time zero to 24 hours after the SC administration. Other PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist.

Plasma PK parameters will be summarized using descriptive statistics by treatment group and IM status. Additional details regarding the PK analysis will be described in the SAP.

Population PK, PK/PD, and covariate analysis may be performed if deemed appropriate, and results will be reported separately.

10.6.4.2 Immunogenicity Analysis

Immunogenicity (IM) results (screen positive/negative, confirmed positive/negative or not evaluable, and when applicable, titer of anti-volanesorsen antibodies) before, during, and after treatment with Study Drug (volanesorsen) (i.e., sample [anti-drug antibody] ADA status) will be listed by their prior treatment in study ISIS 304801-CS6 or ISIS 304801-CS16 (Groups 1 and 2) and study day. Subject ADA status (positive/negative or not evaluable) for all evaluable patients, along with the study day associated with the first positive IM status emerged (T_{first}, i.e., onset of ADA development), the last positive IM status observed (T_{last}), the last ADA sample collection day, and subject - peak titer if applicable, will be listed by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16 (Groups 1 and 2) and study day. Subjects with positive anti-volanesorsen antibody status may be further classified (when applicable) as being either ‘persistent’, ‘transient’, or ‘not determinable’, if deemed appropriate.

Additionally, the sample and subject IM incidence (number) and incidence rate (percent) will be summarized as the total number and percent of evaluated subjects with antibody negative, positive, and unknown status by treatment group. Furthermore, onset and titer of the ADA response, if applicable, will be summarized as median, quartiles (25% and 75%), and range.

Additional details regarding the IM data analysis will be described in the SAP.

Potential relationships between immunogenicity results (e.g., IM status) and selected efficacy (e.g., %change in fasting TG from baseline at 3-, 6-, and 12-month endpoints), safety, and PK (e.g., C_{trough}) measures will be evaluated using graphical analysis and statistical analysis. These analyses will be either conducted and included in the study report, or data pooled and analyzed from all available Phase 2 and 3 studies and reported separately.

11. INVESTIGATOR'S REGULATORY OBLIGATIONS

11.1 Informed Consent

The written informed consent document should be prepared in the language(s) of the potential patient population, based on an English version provided by the Sponsor.

Before a patient's participation in the trial, the Investigator is responsible for obtaining written informed consent from the patient after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific qualification procedures or any Study Drug are administered. The patient must be given sufficient time to consider whether to participate in the study.

The acquisition of informed consent and the patient's agreement or refusal to notify his/her primary care physician should be documented in the patient's medical records and the informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion (not necessarily an Investigator). The original signed informed consent form should be retained in the Study Master File and in any other locations required by institutional policy, and a copy of the signed consent form should be provided to the patient.

11.2 Ethical Conduct of the Study

The Guidelines of the World Medical Association (WMA) Declaration of Helsinki dated October 2002 the applicable regulations and guidelines of current Good Clinical Practice (GCP) as well as the demands of national drug and data protection laws and other applicable regulatory requirements will be strictly followed.

11.3 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent form, other written patient information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by the Sponsor before recruitment of patients into the study and shipment of volanesorsen. A copy of the written approval of any other items/materials that must be approved by the Study Center or IEC/IRB must also be received by the Sponsor before recruitment of patients into the study and shipment of Study Drug. The Investigator's Brochure must be submitted to the IEC/IRB for acknowledgement.

The Investigator must submit to and, where necessary, obtain approval from the IEC/IRB, for all subsequent protocol amendments and changes to the informed consent document. The Investigator should notify the IEC/IRB of deviations from the protocol in accordance with ICH GCP Section 4.5.2. The Investigator should also notify the IEC/IRB of serious adverse events occurring at the Study Center and other adverse event reports received from the Sponsor, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study. Copies of the Investigator's reports, all IEC/IRB submissions and the IEC/IRB continuance of approval must be sent to the Sponsor.

11.4 Patient Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained. On the case report forms (CRF) or other documents submitted to the Sponsor, patients should be identified by unique initials and a patient study number only. Documents that are not for submission to the Sponsor (e.g., signed informed consent forms) should be kept in strict confidence by the Investigator.

In compliance with Federal and local regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the patient to permit named representatives to have access to his/her study-related records without violating the confidentiality of the patient.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments

Protocol amendments must be made only with the prior approval of the Sponsor. Agreement from the Investigator must be obtained for all protocol amendments and amendments to the informed consent document. The regulatory authority and IEC/IRB must be informed of all amendments and give approval for any amendments likely to affect the safety of the patients or the conduct of the trial. The Investigator **must** send a copy of the approval letter from the IEC/IRB to the Sponsor.

12.2 Study Termination

The Sponsor reserves the right to terminate the study according to the terms of the site contract. The Investigator reserves the right to terminate their participation in the study, according to the terms of the site contract. The Investigator/Sponsor should notify the IEC/IRB in writing of the trial's completion or early termination and send a copy of the notification to the Sponsor.

12.3 Study Documentation and Storage

An electronic case report form (eCRF) utilizing an Electronic Data Capture (EDC) application will be used for this study.

The Investigator should ensure that all appropriately qualified persons to whom he/she has delegated trial duties are recorded on a Sponsor-approved Delegation of Site Responsibilities Form.

Source documents are original documents, data, and records from which the patient's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, imaging, and correspondence. In this study, CRFs may not be used as source documents.

The Investigator and Study Center staffs are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation in accordance with Section 8 of the ICH

Guidelines E6 (R2), suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Elements should include:

- Patient files containing completed CRFs, informed consents, and supporting copies of source documentation
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation and all correspondence to and from the IEC/IRB and the Sponsor
- If volanesorsen supplies are maintained at the Study Center, proof of receipt, volanesorsen Accountability Record, Return of volanesorsen for Destruction, final study volanesorsen reconciliation, and all volanesorsen-related correspondence

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

No study document should be destroyed without prior written agreement between the Sponsor or and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor.

12.4 Study Monitoring

The Sponsor representative and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the trial (e.g., CRFs and other pertinent data) provided that patient confidentiality is respected.

The Sponsor monitor is responsible for inspecting the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to patient medical records and other study-related records needed to verify the entries on the CRFs.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's Clinical Quality Assurance Department. Inspection of Study Center facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the trial conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

To ensure the quality of clinical data a clinical data management review will be performed on patient data received by the Sponsor. During this review, patient data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or Study Center notifications will be sent to the Study Center for completion and return to Sponsor.

The Principal Investigator will sign and date the indicated places on the CRF. These signatures will indicate that the principal Investigator inspected or reviewed the data on the CRF, the data queries, and the Study Center notifications, and agrees with the content.

12.5 Language

Case report forms must be completed in English. Generic names for concomitant medications should be recorded in English if possible, unless it is a combination drug, then record the trade name in English.

All written information and other material to be used by patients and investigative staff must use vocabulary and language that are clearly understood.

12.6 Compensation for Injury

The Sponsor maintains appropriate insurance coverage for clinical trials and will follow applicable local compensation laws. Patients will be treated and/or compensated for any study-related illness/injury in accordance with the information provided in the Compensation for Injury section of the Informed Consent document.

13. REFERENCES

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14. APPENDICES

Appendix A Schedule of Procedures

Qualification through Treatment Period

Post-Treatment Follow-up

Extended Treatment Period

Extended Treatment Period Post-Treatment Follow-Up

Appendix A Schedule of Procedures – Qualification through Treatment Period

Study Period		Qual[a]	Treatment Period																					
Study Week		-2 to -1	Wk 1		Wk 4	Wk 6	Wk 8	Wk 10	Month 3		Wk 15 & 17	Wk 19	Wk 21 & 23	Month 6		Wk 28 & 30	Wk 32	Wk 34 & 36	Wk 38	Wk 40 & 42	Wk 44	Wk 46 & 48	Month 12	
									Wk 12	Wk 13				Wk 25	Wk 26								Wk 50	Wk 52 or ET
Study Day		-14 to -7	1	2	22	36	50	64	78	85	99 & 113	127	141 & 155	169	176	190 & 204	218	232 & 246	260	274 & 288	302	316 & 330	344	358
Visit Window+/- Days		0	0	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Informed Consent		X																						
Outpatient Visit		X	X	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X	X[j]	X[j]	X[j]	X[j]	X	X[j]	X[j]	X[j]	X	X[j]	X[j]	X[j]	X[j]	X
Inclusion/Exclusion Criteria		X																						
Medical History[q]		X																						
Vital Signs + body weight (+ height on Day 1 only)		X	X		X		X			X					X				X					X
Physical Examination		X	X							X					X				X					X
12- lead ECG (triplicate)		X								X					X				X					X
MRI (liver/spleen)		X																						X[k]
Echocardiography		X													X[k]									X[k]
Blood Draw (Fasting)[e]	Chemistry Panel	X	X		X		X			X		X			X		X		X		X			X
	CBC with Differential[b]	X	← X → Platelets are assessed each calendar week, visits do not have specified windows to allow flexibility of scheduling.																					
	Serum Lipid Panel	X	X		X		X		X	X				X	X				X				X	X
	Blood viscosity[r]		X							X					X									X
	Platelet aggregation[r]	X	X							X					X									X
	Coagulation (aPTT, PT, INR)	X					X			X					X				X					X
	hsCRP, HbA1c, FPG, and de-lipidated free glycerol	X[n]	X							X					X									X
	Sedimentation Rate		X							X					X									X
	Complement (C5a, Bb)		X							X					X									X
	Plasma PK - Volanesorsen		X[l]	X	X		X			X					X				X					X
	Anti-Volanesorsen Antibodies		X		X		X			X					X				X					X
	FSH (women only, if applicable)	X																						
	Serum Pregnancy Test[d]	X			X		X			X		X			X		X		X		X			X
	Archived Serum & Plasma Samples[e]		X				X			X					X									X
	Troponin I[o]	X																						
	Platelet Bound Autoantibodies[r]		X																					
	Archive blood sample for potential gene sequencing related to hypertriglyceridemia (Group 2 if not available from index study)[g]	X																						

Appendix A Schedule of Procedures - Qualification through Treatment Period *Continued*

Study Period	**Qual[a]**	**Treatment Period**																					
Study Week	**-2 to -1**	**Wk 1**		**Wk 4**	**Wk 6**	**Wk 8**	**Wk 10**	**Month 3**		**Wk 15 & 17**	**Wk 19**	**Wk 21 & 23**	**Month 6**		**Wk 28 & 30**	**Wk 32**	**Wk 34 & 36**	**Wk 38**	**Wk 40 & 42**	**Wk 44**	**Wk 46 & 48**	**Month 12**	
								Wk 12	**Wk 13**				**Wk 25**	**Wk 26**								**Wk 50**	**Wk 52 or ET**
Study Day	**-14 to -7**	**1**	**2**	**22**	**36**	**50**	**64**	**78**	**85**	**99 & 113**	**127**	**141 & 155**	**169**	**176**	**190 & 204**	**218**	**232 & 246**	**260**	**274 & 288**	**302**	**316 & 330**	**344**	**358**
Visit Window+/- Days	**0**	**0**	**0**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
Urinalysis[c]	X	X[m]		X		X			X[m]		X[m]			X[m]		X[m]		X[m]		X[m]			X[m]
Fundus Photography[f]	X																						X[k]
Genetic testing for FCS diagnosis (if not available in medical history)[g]	X																						
Weekly Study Drug: SC Injection		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Symptom Diary (weekly)	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Assessment(s)		X							X					X									X
Food/Drink Diary (quarterly)[h]		X							X					X									X
Diet/Alcohol Counseling[i]	X	X		X		X			X					X				X					X
Adverse Events	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Appendix A Schedule of Procedures – Post-Treatment Follow-up

Study Period		Post Treatment Follow-up[p]				
Study Week		Wk 54 & 56	Wk 58	Wk 65	Wk 71	Wk 78
Study Day		372 & 386	400	449	491	540
Visit Window+/- Days		2	7	7	7	7
Outpatient Visit		X[j]	X[j]	X	X[j]	X
Vital Signs + body weight (+ height on Day 1 only)				X		X
Physical Examination				X		X
12- lead ECG (triplicate)				X		X
Blood Draw (Fasting)[e]	Chemistry Panel		X	X	X	X
	CBC with Differential[b]	X[s]	X	X	X	X
	Serum Lipid Panel			X		X
	hsCRP, HbA1c, FPG, and de-lipidated free glycerol			X		X
	Sedimentation Rate			X		X
	Complement (C5a, Bb)			X		X
	Plasma PK - Volanesorsen			X		X
	Anti-Volanesorsen Antibodies			X		X
	Serum Pregnancy Test[d]		X	X	X	X
	Archived Serum & Plasma Samples[e]			X		X
Urinalysis[c]			X[m]	X[m]	X[m]	X[m]
Symptom Diary (weekly)		X	X	X	X	X
Quality of Life Assessment(s)				X		X
Food/Drink Diary (quarterly)[h]				X		X
Diet/Alcohol Counseling[i]			X	X	X	X
Adverse Events		X	X	X	X	X
Concomitant Medication		X	X	X	X	X

Legend:

a Qualification procedures performed (Please refer to Sections 3.4, 4.1, and 6.1.2)

b Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1 week and the result must be reviewed by the Investigator and confirmed to be acceptable before dosing can continue. All platelet count results will be promptly reviewed by the Investigator to determine if the count has met a stopping rule, or the dose reduction rule of 100,000/mm^3, or the dose pause rule of 75,000/mm^3. Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor

c Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours. During treatment period urine and blood samples will be collected prior to Study Drug administration. Does not apply to 24-hour PK blood draw

d Females of childbearing potential only

e Serum and plasma samples will be collected and stored for follow-up exploration of laboratory findings and/or adverse events (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.) in this or subsequent clinical studies of volanesorsen

f If possible, fundus photography should be completed prior to administration of the first dose of Study Drug (Group 2 ISIS 304801-CS16 roll over patients) and repeated at Week 52 (Please refer to Section 6.2.2.2)

g Genetic testing can be conducted for study Qualification (Group 2 ISIS 304801-CS16 roll over patients); genetic testing will only be conducted if allowed in the geographic region and only after the patient has given specific written informed consent for genetic testing

h In addition to diary, patients will be contacted at random times during the study to review their current eating and drinking habits

i To reinforce compliance to the diet and alcohol restrictions. Random diet/alcohol assessments (phone visits) will also be performed by dietician or study personnel

j Assessments and procedures to be conducted by either a home healthcare nurse, or the Study Center as arranged by the Study Center personnel

k A ± 7-day window is allowed for MRI, echocardiography procedures and fundus photography

l Full or abbreviated PK profile (see Appendix C)

m Expanded urinalysis (see Appendix B)

n HbA1c only

o All abnormal troponin samples will be rerun at the central laboratory and also analyzed for CK-MB

p If needed, the post-treatment follow-up period will be extended (with patients monitored every 6 weeks) until apoC-III levels return to baseline values

q Patient charts will be reviewed in order to collect data for events of acute pancreatitis or suspected pancreatitis in the patient's medical history. Chart review may be conducted at any time during the study. These events will be adjudicated in the same manner as for events of pancreatitis during the study

r May be done. Blood viscosity and platelet aggregation in volanesorsen-treatment naïve patients only

s Platelets are assessed each calendar week, visits do not have specified windows to allow flexibility of scheduling

Appendix A Schedule of Procedures – Extended Treatment Period

Study Period		Extended Treatment Period														
Study Week		**Wk 54 & 56**	**Wk 58**	**Wk 60 & 62**	**Mo 15 Wk 64**	**Wk 66 & 68**	**Wk 70**	**Wk 72 & 74**	**Mo 18 Wk 76**	**Wk 78 & 80**	**Wk 82**	**Wk 84, 86, & 88**	**Mo 21 Wk 90**	**Wk 92 & 94**	**Wk 96**	**Wk 98, 100 & 102**	**Mo 24 Wk 104**
Study Day		**372 & 386**	**400**	**414 & 428**	**442**	**456 & 470**	**484**	**498 & 512**	**526**	**540 & 554**	**568**	**582, 596 & 610**	**624**	**638 & 652**	**666**	**680, 694 & 708**	**722**
Visit Window+/- Days		**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
Outpatient Visit		X[f]	X[f]	X[f]	X	X[f]	X[f]	X[f]	X	X[f]	X[f]	X[f]	X	X[f]	X[f]	X[f]	X
Vital Signs (+ body weight)					X				X				X				X
Physical Examination									X								X
12- lead ECG (triplicate)									X								X
Urinalysis (including P/C ratio)			X		X		X		X		X		X		X		X
Blood Draw (Fasting)[b]	Chemistry Panel		X		X		X		X		X		X		X		X
	CBC with Differential[a]	X Platelets are assessed each calendar week, visits do not have specified windows to allow flexibility of scheduling.															
	Serum Lipid Panel				X				X				X				X
	Coagulation (aPTT, PT, INR)				X				X				X				X
	Troponin I				X				X				X				X
	Plasma PK - ISIS 304801[c]								X								X
	Anti-ISIS 304801 Antibodies								X								X
	Serum Pregnancy Test[d]		X		X		X		X		X		X		X		X
Weekly Study Drug: SC Injection		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Diet/Alcohol Counseling[e]					X				X				X				X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Legend:

a Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1 week and the result must be reviewed by the Investigator and confirmed to be acceptable before dosing can continue. All platelet count results will be promptly reviewed by the Investigator to determine

if the count has met a stopping rule, or the dose reduction rule of 100,000/mm^3, or the dose pause rule of 75,000/mm^3. Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor

b Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours. During treatment period urine and blood samples will be collected prior to Study Drug administration

c Abbreviated PK collection (see Appendix C)

d Females of childbearing potential only

e To reinforce compliance to the diet and alcohol restrictions

f Assessments and procedures to be conducted by either a home healthcare nurse, or the Study Center as arranged by the Study Center personnel

Appendix A Schedule of Procedures – Extended Treatment Period (Post-Treatment Follow-Up)

Study Period		**Post Treatment Follow-up[a]**				
Study Week		**Wk 106 & 108**	**Wk 110**	**Wk 117**	**Wk 123**	**Wk 130**
Study Day		**736 & 750**	**764**	**813**	**855**	**904**
Visit Window+/- Days		**2**	**7**	**7**	**7**	**7**
Outpatient Visit		X[b]	X[b]	X	X[b]	X
Vital Signs + body weight (+ height on Day 1 only)				X		X
Physical Examination				X		X
12- lead ECG (triplicate)				X		X
Blood Draw (Fasting)[e]	Chemistry Panel		X	X	X	X
	CBC with Differential[c]	X[d]	X	X	X	X
	Serum Lipid Panel			X		X
	hsCRP, HbA1c, FPG, and de-lipidated free glycerol			X		X
	Sedimentation Rate			X		X
	Complement (C5a, Bb)			X		X
	Plasma PK - Volanesorsen			X		X
	Anti-Volanesorsen Antibodies			X		X
	Serum Pregnancy Test[f]		X	X	X	X
	Archived Serum & Plasma Samples[g]			X		X
Urinalysis			X[h]	X[h]	X[h]	X[h]
Symptom Diary (weekly)		X	X	X	X	X
Quality of Life Assessment(s)				X		X
Diet/Alcohol Counseling[i]			X	X	X	X
Adverse Events		X	X	X	X	X
Concomitant Medication		X	X	X	X	X

Legend:

a If needed, the post-treatment follow-up period will be extended (with patients monitored every 6 weeks) until apoC-III levels return to baseline values

b Assessments and procedures to be conducted by either a home healthcare nurse, or the Study Center as arranged by the Study Center personnel

c Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1 week and the result must be reviewed by the Investigator and confirmed to be acceptable before dosing can continue. All platelet count results will be promptly reviewed by the Investigator to determine if the count has met a stopping rule, or the dose reduction rule of 100,000/mm^3, or the dose pause rule of 75,000/mm^3. Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor

d Platelets are assessed each calendar week, visits do not have specified windows to allow flexibility of scheduling

e Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours. During treatment period urine and blood samples will be collected prior to Study Drug administration. Does not apply to 24-hour PK blood draw

f Females of childbearing potential only

g Serum and plasma samples will be collected and stored for follow-up exploration of laboratory findings and/or adverse events (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.) in this or subsequent clinical studies of volanesorsen

h Expanded urinalysis (see Appendix B)

i To reinforce compliance to the diet and alcohol restrictions. Random diet/alcohol assessments (phone visits) will also be performed by dietician or study personnel

Appendix B List of Laboratory Analytes

Appendix B List of Laboratory Analytes

Based on emerging data from this or future studies, additional tests not listed below may be performed on stored samples to better characterize the profile of volanesorsen or other similar oligonucleotides.

Clinical Chemistry Panel

- Sodium
- Potassium
- Chloride
- Bicarbonate
- Total protein
- Albumin
- Calcium
- Magnesium
- Phosphorus
- Glucose
- BUN
- Creatinine
- Uric Acid
- Total bilirubin
- Direct (conjugated) bilirubin
- Indirect (unconjugated) bilirubin
- ALT
- AST
- Alkaline phosphatase

Coagulation

- aPTT (sec)
- PT (sec)
- INR

Lipid Panel

- Total Cholesterol
- LDL-C
- HDL-C
- Triglycerides
- Non-HDL-C
- VLDL-C
- apoA-1
- apoB
- apoC-III

Hematology

- Red blood cells
- Hemoglobin
- Hematocrit
- MCV, MCH, MCHC
- Platelets
- White blood cells
- WBC Differential (% and absolute)
  - Neutrophils
  - Eosinophils
  - Basophils
  - Lymphocytes
  - Monocytes

Pharmacokinetics[1] & Immunogenicity

- Volanesorsen levels in plasma
- Anti-volanesorsen antibodies in plasma

Other Assessments

- hsCRP
- Sedimentation Rate
- C5a, Bb
- Troponin I[2]
- CK-MB[2]
- Platelet Bound Autoantibodies[3]
- De-lipidated free glycerol
- HbA1c, FPG
- Blood viscosity[3]

Urinalysis

- Color
- Appearance
- Specific gravity
- pH
- Protein
- Blood
- Ketones
- Urobilinogen
- Glucose
- Bilirubin
- Leukocyte esterase
- Nitrate
- Microscopic examination[4]

Additional Measures for Expanded Urinalysis

- Total protein (quantitative)
- Microalbumin
- β2-microglobulin

Platelet Function

- Platelet aggregation[3]

1 Plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, IM testing (or possibly for purposes of IM assay development and/or validation), or to assess other actions of volanesorsen with plasma constituents

2 All abnormal troponin samples will be rerun at the central laboratory and also analyzed for CK-MB

3 May be done

4 Will be performed on abnormal findings unless otherwise specified

Appendix C Pharmacokinetic Sampling Schedule

Appendix C Pharmacokinetic Sampling Schedule

Blood samples for the determination of plasma volanesorsen concentrations will be collected prior to dosing, and at various times throughout the dosing and post-treatment follow-up period as noted in the tables below.

PK Sampling Schedule (All Patients except PK Subgroup)

Week	Wk 1	Wk 4	Wk 8	Wk 13	Wk 26	Wk 38	Wk 52	Wk 65	Wk 78
Study Day	**D1**	**D22**	**D50**	**D85**	**D176**	**D260**	**D358**	**D449**	**D540**
Visit Window +/- Days	0	2	2	2	2	3	2	7	7
Time Point	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime	Anytime

PK Sampling Schedule (PK Subgroup only*)

Week	Wk 1	Wk 1	Wk 4	Wk 8	Wk 13	Wk 26	Wk 38	Wk 52	Wk 65	Wk 78
Study Day	**D1**	**D2**	**D22**	**D50**	**D85**	**D176**	**D260**	**D358**	**D449**	**D540**
Visit Window +/- Days	0	0	2	2	2	2	3	2	7	7
Time Point	Pre-dose, 1, 2, 3, 4, 6, 8, and 12 hrs post-dose	24 hrs Post-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime	Anytime

* Patients at selected sites will be asked to participate in the extended 24-hour PK profile beginning on Study Day 1. Participation is optional

PK Sampling Schedule (Extended Treatment Period)

Week	Wk 76	Wk 104	Wk 117
Study Day	**D526**	**D722**	**D813**
Visit Window +/- Days	2	2	7
Time Point	Pre-dose	Pre-dose	Anytime

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

The following grading recommendations for adverse events relating to lab test abnormalities are based upon the **Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010**

Adverse Event	Mild	Moderate	Severe
Hematology			
aPTT prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage
Eosinophils increased†	650 – 1,500 cell/mm^3	1,501 - 5,000 cell/mm^3	>5,000 cell/mm^3
Fibrinogen decreased	<1.0 - 0.75 x LLN or <25% decrease from baseline	<0.75 - 0.5 x LLN or 25 - <50% decrease from baseline	<0.5 x LLN or ≥50% decrease from baseline
Hemoglobin decreased (Anemia)	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated
Hemoglobin increased	Increase in >0 - 2 g/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 g/dL above ULN or above baseline if baseline is above ULN	Increase in >4 g/dL above ULN or above baseline if baseline is above ULN
INR increased	>1 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation
Lymphocyte count decreased	<LLN - 800/mm^3; <LLN - 0.8 x 10^9/L	<800 - 500/mm^3; <0.8 - 0.5 x 10^9 /L	<500 /mm^3; <0.5 x 10^9 /L
Lymphocyte count increased	-	>4000/mm^3 - 20,000/mm^3	>20,000/mm^3
Neutrophil count decreased	<LLN - 1500/mm^3; <LLN - 1.5 x 10^9 /L	<1500 - 1000/mm^3; <1.5 - 1.0 x 10^9 /L	<1000/mm^3; <1.0 x 10^9 /L
Platelet count decreased	<LLN - 75,000/mm^3; <LLN - 75.0 x 10^9 /L	<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9 /L	<50,000/mm^3; <50.0 x 10^9 /L
White blood cell decreased	<LLN - 3000/mm^3; <LLN - 3.0 x 10^9 /L	<3000 - 2000/mm^3; <3.0 - 2.0 x 10^9 /L	<2000/mm^3; <2.0 x 10^9 /L
Chemistry			
Acidosis	pH <normal, but **>=**7.3	-	pH <7.3
Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Alkalosis	pH >normal, but ≤7.5	-	pH >7.5
Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 x ULN
Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

Adverse Event	Mild	Moderate	Severe
Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer
CD4 lymphocytes decreased	<LLN - 500/mm^3; <LLN - 0.5 x 10^9 /L	<500 - 200/mm^3; <0.5 - 0.2 x 10^9 /L	<200/mm^3; <0.2 x 10^9 /L
CPK increased*	>ULN - <6 ULN	6 - 10 x ULN	>10 x ULN
Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 x ULN
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 mg/dL; >3.1 mmol/L; Ionized calcium >1.6 mmol/L; hospitalization indicated
Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 mg/dL; >13.9 mmol/L; hospitalization indicated
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0; hospitalization indicated
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 mg/dL; >1.23 mmol/L
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 mmol/L; hospitalization indicated
Hyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 mg/dL; <1.75 mmol/L; Ionized calcium <0.9 mmol/L; hospitalization indicated
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 mg/dL; <3.0 mmol/L	<40 mg/dL (<2.2 mmol/L) AND requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions‡
Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 mmol/L; hospitalization indicated
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 mg/dL; <0.4 mmol/L
Hyponatremia	<LLN - 130 mmol/L	-	<130 mmol/L
Hypophosphatemia	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 mg/dL; <0.6 mmol/L
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

Adverse Event	Mild	Moderate	Severe
Urine			
Proteinuria Adults Children	1+ proteinuria; urinary protein <1.0 g/24 hrs -	2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs; Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Urinary protein ≥3.5 g/24 hrs; Urine P/C >1.9
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated

†Grading for this parameter is derived from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007

*Grading for this parameter is derived from the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0, Nov 2014

‡Modified for consistency with the ADA and Endocrine Society Guidelines (Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. Diabetes Care 2013;36:1384-95)

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ISIS 304801-CS7

The APPROACH Open-Label Study

Volanesorsen (ISIS 304801)

An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol Amendment 8 – 21 November 2018

EudraCT No: 2015-003755-21

ISIS 304801-CS7

The APPROACH Open-Label Study

Volanesorsen (ISIS 304801)

An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol Amendment 8 – 21 November 2018

Protocol History:

Original Protocol:	28 August 2015
Protocol Amendment 1:	2 February 2016
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Protocol Amendment 7:	7 April 2017

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Ionis Protocol Number: ISIS 304801-CS7

Protocol Amendment 8

EudraCT No: 2015-003755-21

Clinical Phase: 3

The APPROACH Open-Label Study

Volanesorsen (ISIS 304801)

An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

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Date: 21 November 2018

Confidentiality Statement

This document contains confidential information of Akcea Therapeutics, Inc. and Ionis Pharmaceuticals, Inc., that must not be disclosed to anyone other than the recipient study staff and members of the independent ethics committee, institutional review board, or authorized regulatory agencies. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Akcea Therapeutics, Inc. and Ionis Pharmaceuticals, Inc.

Protocol Signature Page

Protocol Number:	ISIS 304801-CS7
Protocol Title:	An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Amendment:	Amendment 8
Date:	21 November 2018

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)", dated 21 November 2018, and agree to conduct the study as described herein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice (E6) (R2).

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Akcea Therapeutics, Inc. and Ionis Pharmaceuticals, Inc.

Investigator's Signature

Investigator's Name *(please print)*

Date (DD Month YYYY)

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PROTOCOL AMENDMENT

Protocol Number:	ISIS 304801-CS7
Protocol Title:	An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Amendment Number:	8
Amendment Date:	21 November 2018

The purpose of this protocol amendment is to implement the following modifications to Protocol ISIS 304801-CS7 Amendment 7 dated 7 April 2017:

- To add the option for patients to receive a study drug dose reduction as either 300 mg every two weeks (prefilled syringe) or 150 mg once-weekly (vial presentation), to clarify that discontinuation from the treatment period will be required for any patients who are on a dose pause for ≥ 3 months, and to remove the references to landmark visits (if patient stops drug treatment then they enter the follow-up period).

Minor changes (not included in the list of changes below) have been made throughout the protocol to correct errors and/or to improve the overall clarity of the original protocol but these changes do not impact subject safety, exposure, or the overall study design.

The following table provides a summary list of major changes to the protocol, additions are indicated as underline and deletions are indicated as strikethrough:

Protocol Section	Description of Change	Rationale
Section 2.3.4 Clinical experience	~~Volanesorsen has been evaluated in one Phase 1 study and two Phase 2 studies, all double blinded and placebo controlled. The total exposures comprise 99 patients and healthy volunteers administered volanesorsen from 50 to 400 mg subcutaneously up to 3 months (compared to 37 administered placebo).~~ The clinical experience with volanesorsen includes clinical trials in healthy subjects, patients with hypertriglyceridemia, FCS, or familial partial lipodystrophy. Overall, 431 patients and healthy volunteers have taken part in the clinical development program, of whom 325 have received at least 1 dose of volanesorsen. Ninety-five (95) patients with FCS have been enrolled in studies, all showing clinically meaningful reductions in plasma triglyceride. Patients with FCS continue on treatment in the open-label extension (OLE) and triglyceride reductions persist at similar levels as reported in earlier studies. In the completed Phase 1 and Phase 2 studies, volanesorsen was well-tolerated and demonstrated a favorable safety profile. There was no clinical or laboratory evidence of drug-drug interactions despite many patients in the Phase 2 clinical trials receiving	Update to language regarding clinical experience in Phase 1 and 2 studies and incidence of AEs in completed Phase 3 studies and update to language regarding safety risks of Study Drug.

	concomitant medications that are known to be associated with elevations in hepatic enzymes, such as fibrates and statins. There were no volanesorsen-associated laboratory abnormalities suggestive of an effect on the renal (serum creatinine, proteinuria) or hepatic systems (alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin). There was a reduction (mean reduction < 30%) in platelets in volanesorsen vs. placebo with mean nadirs for all doses remaining above the lower limit of normal (LLN). The most frequently reported adverse events (AEs) were mild, non-progressive events at the injection site. In Phase 2, a single serious adverse event (SAE) of secondary serum sickness-like reaction was reported as related to Study Drug. ... ~~In clinical studies conducted to date volanesorsen has been well-tolerated and has shown a favorable safety profile. There has been no clinical or laboratory evidence of drug-drug interactions.~~ ~~In the completed studies there have been no volanesorsen-associated laboratory abnormalities suggestive of an effect on the renal (serum creatinine, proteinuria) or hepatic systems (alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin). In Phase 2 studies, there was a mild decrease of platelet count associated with volanesorsen administration that recovered in the post-treatment period and was not associated with platelet-related adverse events (AEs). In the blinded ongoing clinical trials of ISIS 304801, 2 patients of 142 dosed (as of February 29, 2016) had a decrease in platelet count to less than 50,000/mm3 in the absence of major bleeding or clinically-relevant non-major bleeding and had Study Drug paused as per the monitoring and stopping rules for platelet counts (Section 8.6.3). Platelet counts recovered following suspension of treatment.~~ ~~The most frequently observed AEs with volanesorsen were local reactions at the injection site. Local cutaneous reactions at the injection site defined as those events presenting as either pain, tenderness, erythema, pruritus or swelling occurring on the day of injection and persisting for at least 2 days were infrequent (~15% of injections), were almost always mild, resolved spontaneously, were non-progressive, and were not associated with systemic sequelae.~~ In the completed pooled Phase 3 studies (ISIS 304801-CS6 (hereafter CS6) and ISIS 304801-CS16 (hereafter CS16), the most common AEs associated with volanesorsen administration were tolerability at the injection site and platelet reductions. The majority of the injection site AEs were mild, none were severe, and the incidence appeared to decrease over time. No deaths have been associated with volanesorsen treatment to date. No cardiac toxicity was associated with volanesorsen treatment. There were no abnormal QTc findings and no study-drug related adjudicated major adverse cardiac events (MACE). There is no evident association between volanesorsen treatment and changes in renal or liver functions.	

	~~In conclusion,t~~ The safety profile of volanesorsen has been well-described in this development program, which has identified 3 safety risks: thrombocytopenia (an identified risk), constitutional symptoms (flu-like reactions and influenza-like illness), and injection site reactions (a tolerability signal). Spontaneous, mild to severe thrombocytopenia has been described in the FCS patient population (Gaudet et al. 2017),but is increased by treatment with volanesorsen. Less frequent and less pronounced platelet declines were also observed with volanesorsen treatment in the hypertriglyceridemic (HTG) population of CS16. When fully complied with, frequent monitoring for this effect and appropriate dose adjustments have been successful both in preventing or promptly detecting the occurrence of severe platelet declines and often in retaining patients on treatment.	
Section 2.4 Rationale for Dose and Schedule of Administration	The dose and schedule selected for this study is 300 mg per week for 52 weeks. The dose of 300 mg per week and dose reduction to 300 mg every 2 weeks (delivered as either a single 300-mg dose or as 150 mg once-weekly, respectively) are ~~is~~ supported by both the cumulative nonclinical data available to date and the Phase and 3 clinical data. … Non nonclinical findings were not considered to be related to the pharmacologic inhibition of apoC-III.	Language added to specify dose reductions as either 300 mg every 2 weeks or 150 mg weekly according to patient's tolerability on the 300 mg dose, given similar extents of triglyceride lowering anticipated based on population pharmacokinetic/pharmacodynamic model based simulations.
Section 3.4.4 Post-Treatment	Patients not participating in the extended treatment period will enter the post-treatment evaluation period ~~is~~ **of** 13 weeks ~~and, consists~~ consisting of 7 Study Center visits on Weeks 53, 54, 55, 56, 57, 58, and 65 (Weeks 53, 54, 55, 56, 57, and 58 may be conducted by a home healthcare nurse). Patients who complete, or terminate early from, the extended treatment period without subsequently participating in an expanded access program will enter a 13-week post-treatment evaluation period consisting of 7 Study Center visits on Weeks 105, 106, 107, 108, 109, and 110 (which may be conducted by a home healthcare nurse), and Week 117 (Appendix A).	Language added to specify that patients who discontinue from treatment during treatment period of the study, who previously would have been followed for landmark visits, will now enter into the 13-week follow-up period
Section 6.1.3 Treatment Period Synopsis, Study Visits and Procedures	Collection and measurement of race and ethnicity, vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), adverse events (AE), concomitant medication/procedure information, lipid panel, blood viscosity, volanesorsen plasma concentrations, immunogenicity (IM) testing, platelet aggregation, liver/spleen magnetic resonance imaging (MRI), ECGs, echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A.	To add a specification that race and ethnicity are to be collected.
Section 6.2.1 Laboratory Assessments	Should a patient experience constitutional or flu-like symptoms after Study Drug administration, investigators may consider additional laboratory assessments. For example, plasma and serum samples may be drawn for complement (Total C3, C4, C5a and Bb), hsCRP and for cytokine analysis.	To add additional laboratory assessments permitted for safety purposes
Section 7.1 Volanesorsen Description	… Volanesorsen (ISIS 304801) is contained in glass prefilled syringes (PFS) or in glass vials. Table 1 Volanesorsen (ISIS 304801) Characteristics	To add details of study drug preparation to be used in the open-label extension phase

	<table><tr><td>Study Drug</td><td>ISIS 304801 Prefilled Syringe</td><td>ISIS 304801 Vial*</td></tr><tr><td>Strength</td><td>300 mg</td><td>200 mg</td></tr><tr><td>Volume / Formulation</td><td>1.5 mL 200 mg/mL ISIS 304801</td><td>1.0 mL 200 mg/mL ISIS 304801</td></tr><tr><td>Dose</td><td>300 mg / 1.5 mL</td><td>150 mg / 0.75 mL</td></tr><tr><td>Route of Administration</td><td>Subcutaneous injection</td><td>Subcutaneous injection</td></tr></table>	
Section 7.3 Study Drug Accountability	All used syringes or vials must be disposed of as per the site's hazardous waste destruction policy.	Specified disposal of study drug preparation to be used in the open-label extension phase
Section 8.1 Volanesorsen Administration	For each individual patient, volanesorsen will be administered subcutaneously as a single 1.5 mL 300 mg injection once weekly for Weeks 1-52, and patients will continue to receive Study Drug as a single 300 mg/1.5 mL injection once-weekly for Weeks 53-104 of the study. Patients entering this ISIS 304801-CS7 study on a reduced dose or dose frequency of Study Drug (volanesorsen), for safety or tolerability reasons in their index study (ISIS 304801-CS6 or ISIS 304801-CS16), will receive a reduced dose or dose frequency of volanesorsen for continued safety or tolerability as outlined in Sections 8.5 and 8.6. Patients on dose reduction will receive either 300 mg/1.5 mL injections every 2 weeks or 150 mg/0.75 mL injections once-weekly. Treatment with a 150 mg dose during the study will use the glass vials containing 200 mg/mL of volanesorsen. ~~Patients entering this CS7 study having dose or dose frequency reduced in the CS16 index study after 13 weeks of treatment, as outlined in CS16 Amendment 4 Section 8.7, can receive the 300 mg once weekly dose of volanesorsen.~~ **Treatment** Patients should receive 1 dose per week, unless on a dose reduction of 300 mg every 2 weeks, with weeks always defined relative to Study Day 1. …	Added language detailing dose reduction options.
Section 8.5.2 Safety Monitoring for Platelet Count Results	Monitor every 1 week unless otherwise specified. In addition, platelet function may be evaluated at any time during the study by aggregometry, using an approved point-of-care diagnostic device in some patients. This additional functional testing may be performed at selected study centers. … Due to the 1 to 2-year study duration, it is anticipated that patients may undertake travel including vacations, which may impede weekly platelet monitoring. In some situations, it may be possible to arrange for local laboratory testing or use of the home healthcare service at their temporary location. The intent is to maintain weekly platelet monitoring and treatment where possible, as well as Investigator site contact with the study patients. However, if the above options are not possible, a temporary interruption of study treatment will be	Additional point-of-care platelet function testing may be conducted on patients at participating study centers. Included an additional blood draw to assess platelet count prior to any travel that would result in missing a weekly monitoring visit.

	planned with a platelet count drawn within 3-5 days prior to departure **and** a prompt blood draw upon the patient's return which must be reported and reviewed by the Investigator prior to the patient resuming treatment. Patients on dose pause should be monitored as per the platelet monitoring rules outlined in Section 8.8.1 until Study Drug administration is resumed.	
8.5.4 Safety Monitoring for Constitutional Symptoms	Should a patient experience constitutional or flu-like symptoms after Study Drug administration, investigators may consider additional laboratory assessments. For example, plasma and serum samples may be drawn for complement (Total C3, C4, C5a and Bb), hsCRP, and for cytokine analysis.	To add additional laboratory assessments permitted for safety purposes
Section 8.6.3 Stopping Rules for Platelet Count Results	In the event of any platelet count less than 50,000/mm^3, or a platelet count less than 75,000/mm^3 that occurs while the patient is treated at 300 mg every 2 weeks or 150 mg once-weekly then treatment of a patient with volanesorsen will be stopped permanently. … In the event of a platelet count less than 75,000/mm^3, and in the absence of major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), treatment of a patient with volanesorsen should be suspended temporarily until the platelet count has recovered to ≥ 100,000/mm^3. If ~~dosing is continued~~ treatment is reinitiated, it should be at a reduced dose frequency of 300 mg every 2 weeks or 150 mg once-weekly ~~every week~~(refer to Section 8.7). Table 3 Actions in Patients with Low Platelet Count or Drop in Platelet Count	To provide clarification to the platelet safety monitoring rules, including dose reduction options.

Platelet Count on Rx	Drug Dose	Monitoring
	Study Drug administration is contingent on the availability of the immediately preceding test result. An interpretable platelet value must be available within 7 days prior to treatment. Only the study doctor or qualified designee can authorize continued Study Drug administration based on an acceptable platelet value. Patients should not administer a dose until they have been contacted by their study doctor or designee and told that it is acceptable to dose. Authorization to dose must be documented in the patient's medical records.	Monitor every 1 week unless otherwise specified In addition, platelet function may be evaluated during the study by aggregometry, using an approved point-of-care diagnostic device, in some patients. This additional functional testing may be performed at selected study centers. Patients on dose pause should be monitored as per the platelet monitoring rules outlined in Section 8.8.1 until Study Drug administration is resumed. Obtain additional lab tests (Table 2) if 2 occurrences (consecutive or non-consecutive) of platelet count 140K - > 100K/mm^3 or 1 occurrence of platelet count ≤ 100K/mm^3. Labs only need to be performed once. Labs may be collected over multiple visits, if blood requirements are a concern, as per Investigator discretion.

	> 100K/mm^3	Once -weekly 300 mg Study Drug administration		
	100K/mm^3 - > 75K/mm^3	Permanently reduce dose frequency to 300 mg every 2 weeks or 150 mg once-weekly.		
	75K/mm^3 - > 50K/mm^3	• If occurs while on dose of 300 mg every 2 weeks or 150 mg once-weekly then permanently discontinue Study Drug, otherwise dose pause. If dose pause is ≥ 3 months then patient must discontinue treatment and enter the follow up period. • When platelet count returns to > 100K/mm^3 restart treatment at dose frequency of 300 mg every 2 weeks or 150 mg once-weekly ~~only if approved by~~ in consultation with the Sponsor Medical Monitor	Monitor every 2-3 days until 2 successive values are > 75K/mm^3 then monitor every 1 week Consider discontinuation of antiplatelet agents/NSAIDS/ anticoagulant medication	

	≤ 50K/mm^3	Permanently discontinue Study Drug and the patient will enter the follow up period.	• Monitor daily until 2 successive values show improvement then monitor every 2-3 days until 2 successive values are > 75K/mm^3 then monitor every 1 week • Patient should be evaluated by a hematologist to provide diagnostic and therapeutic management • Steroids recommended*. It is strongly recommended that, unless the patient has a medical contraindication to receiving glucocorticoids, the patient receives glucocorticoid therapy to reverse the platelet decline. • Monitor triglyceride levels weekly and continue AE monitoring during steroid therapy Discontinue antiplatelet agents/ NSAIDS/ anticoagulant medication while platelet count is < 50K/mm^3 if possible	
Section 8.7 Adjustment of Dose Frequency	Other dose adjustments, including dose interruptions, and/or decreasing the dose to 150 mg once-weekly or the dose frequency to 300 mg every 2 ~~other~~ weeks will be allowed for safety and tolerability.			Addition of dose reduction options to allow for safety and tolerability Discontinuation of patients from the

	… Patients may be dose paused in response to AEs ~~after consultations with~~, and the Study Medical Monitor is informed. If a patient is dose paused for ≥ 3 months, he or she is considered to have discontinued treatment and should enter the 13-week post-treatment follow-up period.	study who have been on dose pause and off study drug for >3 months.
Section 8.8 Discontinuation of Study Treatment	A patient must permanently discontinue study treatment for any of the following: … •The patient is dose-paused for ≥ 3 months ~~then they must discontinue the treatment period and enter the follow-up period~~.	Added new treatment discontinuation criterion consistent with other protocol changes.
Section 8.8.1 Follow-up Visits for Early Termination from Treatment Period	~~Patients should be strongly encouraged to attend applicable landmark visits at Weeks 12, 13, 25, 26 and 50, 52 of Randomized Treatment period (calculated based on the time elapsed since Day 1) and at Weeks 64, 65, 77, 78 and 102, 104 of OLE period to collect fasting lipid panels and conduct safety assessments in accordance with the schedule of procedures in Appendix A.~~ Any patient who discontinues treatment after Week 44 should also be strongly encouraged to attend a final follow-up visit (Week 65 visit assessments) approximately 13 weeks after their last dose of Study Drug~~, in addition to the applicable landmark visits~~. … A patient who discontinues early from treatment with stable platelet counts above the LLN at the time of treatment discontinuation will have platelet counts drawn every 2 weeks after discontinuing Study Drug for the first 6 weeks after the last dose of Study Drug. A subsequent platelet count should then be taken after an additional 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug.	Removal of language around landmark visits as patients who stop treatment now enter a post-treatment follow-up period Provides guidance for platelet monitoring in the post-treatment follow-up period.
Section 13 REFERENCES	Gaudet D, Baass A, Tremblay K, et al. Natural History (up to 15 years) of Platelet Count in 84 Patients with Familial Hyperchylomicronemia Due to Lipoprotein Lipase Deficiency. Journal of Clinical Lipidology 2017; 11(3): 797-798.	Addition of reference
Section 14 APPENDICES	Appendix A Schedule of Procedures Added platelet function analysis to extended treatment period table. Footnote i: Genetic testing can be conducted for study qualification (Group 2 [ISIS 304801-CS16 roll-over patients] and Group 3); genetic testing will only be conducted if allowed in the geographic region and only after the patient has given specific written informed consent for genetic testing. A blood sample for potential gene sequencing may be collected at timepoints other than Screening or Qualification Visits.Footnote g: May be done	Clarification that blood sampling for gene sequencing may occur during the study. Indication that platelet function may be assessed.
Section 14 APPENDICES	**Appendix B List of Laboratory Analytes** Platelet Function Platelet aggregation[3] Platelet function[5]	Addition of laboratory analyte to measure platelet function.

	Footnote 5: May be done using a point-of-care device on site.	

PROTOCOL SYNOPSIS

Protocol Title	An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Study Phase	3
Indication	Familial Chylomicronemia Syndrome
Study Objectives	To evaluate the safety and efficacy of treatment and extended treatment with volanesorsen in patients with FCS
Study Design	This is a multi-center open-label study of: Group 1: ISIS 304801-CS6 (index study) roll-over FCS patients Group 2: ISIS 304801-CS16 (index study) roll-over FCS patients Group 3: FCS patients who did not participate in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies All patients will receive volanesorsen 300 mg once per week for 52 weeks. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period. Following the Week 52 visit, patients will have the option of participating in an expanded access program or continuing treatment for up to an additional 52 weeks until an expanded access program is approved and available in their country. Patients not participating in an expanded access program will enter a 13-week post-treatment evaluation period
Number of Patients	Up to approximately 70 patients dosed
Study Population	Inclusion Criteria: 1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law 2. Age ≥ 18 years at time of informed consent 3. Groups 1 and 2: Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement. Groups 2 and 3: Patients must also meet the following criteria in order to enter into the open-label study: a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L) b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) supported by documentation of at least 1 of the following: • Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1) • Post heparin plasma LPL activity of ≤ 20% of normal in medical history. Note: testing of LPL activity should not be performed to confirm eligibility for the study

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	c. Group 2: Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 index study Group 3: Fasting TG ≥ 750 mg/dL at Screening for this open-label study 4. Able and willing to participate in a 65-week studyInclusion Criteria: *Continued* 5. Satisfy 1 of the following: a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved), abstinent*, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration b. Males: Surgically sterile, abstinent* or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration * Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception Exclusion Criteria for Group 1 (ISIS 304801-CS6) and Group 2 (ISIS 304801-CS16) Index Study Roll-over Patients 1. Have any new condition or worsening of existing condition which in the opinion of the Investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study 2. Unwilling to comply with lifestyle requirements for the duration of the study (Section 6.3) Exclusion Criteria for Group 3 (patients who did not participate in an index study) 1. Diabetes mellitus with any of the following: a. Newly diagnosed within 12 weeks of screening b. HbA1c ≥ 9.0% at Screening c. Recent change in anti-diabetic pharmacotherapy (change in dosage or addition of new medication within 12 weeks of screening [with the exception of ± 10 units of insulin]) d. Anticipated need to change dose or type of medication during the treatment period of the Study (with the exception of ± 10 units of insulin) e. Current use of GLP-1 agonists

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	2. Severe hypertriglyceridemia other than due to familial chylomicronemia syndrome 3. Active pancreatitis within 4 weeks prior to screening Exclusion Criteria for Group 3 (patients who did not participate in an index study) *Continued* 4. History within 6 months of screening of acute or unstable cardiac ischemia (myocardial infarction, acute coronary syndrome, new onset angina), stroke, transient ischemic attack or unstable congestive cardiac failure requiring a change in medication or major surgery within 3 months of screening 5. Any of the following laboratory values at Screening a. Hepatic: • Total bilirubin > upper limit of normal (ULN), unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL • ALT > 2.0 x ULN • AST > 2.0 x ULN b. Renal: • Persistently positive (2 out of 3 consecutive tests ≥ 1+) for protein on urine dipstick. In the event of a positive test eligibility may be confirmed by a quantitative total urine protein measurement of < 500 mg/24 hrs • Persistently positive (2 out of 3 consecutive tests ≥ trace positive) for blood on urine dipstick. In the event of a positive test eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field • Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault < 50 mL/min (MDRD or CKD-EPI formulas can be used instead of Cockcroft-Gault for estimation of GFR in patients with low body weight after discussion with Sponsor Medical Monitor) c. Platelet count < lower limit of normal (LLN) for the central laboratory (i.e., < 140,000/mm^3) d. Cardiac Troponin I > ULN at Screening e. LDL-C > 130 mg/dL at Screening f. Any other laboratory abnormalities which, in the opinion of the Investigator or the Sponsor, would make the patient unsuitable for inclusion 6. Uncontrolled hypertension (BP > 160/100 mm Hg) 7. History of bleeding diathesis or coagulopathy or clinically-significant abnormality in coagulation parameters at Screening 8. History of heart failure with NYHA greater than Class II 9. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1 10. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B

PROTOCOL SYNOPSIS *Continued*

	11. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated
	12. Treatment with another investigational drug, biological agent, or device within 1 month of screening, or 5 half-lives of investigational agent, whichever is longer Exclusion Criteria for Group 3 (patients who did not participate in an index study) *Continued* 13. Unwilling to comply with lifestyle requirements (Section 6.3) 14. Use of any of the following: a. Statins, omega-3 fatty acids (prescription and OTC), or fibrates unless on a stable dose for at least 3 months prior to screening and dose and regimen expected to remain constant during the treatment period. Patients taking OTC omega-3 fatty acids should make every effort to remain on the same brand throughout the study b. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to screening c. Systemic corticosteroids or anabolic steroids within 6 weeks prior to screening unless approved by the Sponsor Medical Monitor d. Atypical antipsychotic medications (e.g., olanzapine and clozapine) unless on a stable dose for at least 3 months prior to screening and dose and regimen expected to remain stable throughout the study e. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to screening and dose and regimen expected to remain constant during the treatment period f. Glybera gene therapy within 2 years prior to screening g. Oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, and apixaban) unless on a stable dose for at least 4 weeks prior to screening and regular clinical monitoring is performed h. Tamoxifen, estrogens or progestins unless on a stable dose for at least 4 months prior to screening and dose and regimen expected to remain constant during the treatment period i. Plasma apheresis within 4 weeks prior to screening or planned during the study j. Prior exposure to ISIS 304801 k. Any other medication unless stable at least 4 weeks prior to screening (Occasional or intermittent use of over-the-counter medications will be allowed at Investigator's discretion) 15. Blood donation of 50 to 499 mL within 30 days of screening or of > 499 mL within 60 days of screening 16. Known hypersensitivity to any of the excipients of the Study Drug (ISIS 304801 or placebo) 17. Have any other conditions, which, in the opinion of the Investigator or the Sponsor would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the study

PROTOCOL SYNOPSIS *Continued*

Treatment Group	Volanesorsen 300 mg once per week
Study Drug Administration	Volanesorsen will be administered as subcutaneous (SC) injections.
Dose Adjustments	Dose adjustments, including dose interruptions and/or decreasing the dose frequency will be allowed for safety or tolerability after consultation with the Sponsor Medical Monitor.
Rationale for Dose and Schedule Selection	The dose of 300 mg once weekly was chosen for the double-blinded placebo-controlled Phase 3 index studies (ISIS 304801-CS6 and ISIS 304801-CS16) based on the pharmacodynamic and safety analysis of the Phase 2 and 3 studies (Section 2.4) which included a subset of patients with FCS. The same dose of 300 mg once weekly will be used in this open-label study of FCS patients.
Study Visit Schedule and Procedures	The study for an individual patient will generally consist of the following periods: • Group 1 and 2 patients (participated in ISIS 304801-CS6 or ISIS 304801-CS16 index study): A qualification period of up to 2 weeks (unless approved by the Sponsor). Please refer to Section 4.1 and Appendix A • Group 3 patients (did not participate in an index study): An up to 8-week screening and qualification period, including a diet stabilization period of at least 6 weeks (screening and diet stabilization period may be reduced, per Sponsor approval, if the patient is following a diet for optimal control of TGs and disease management prior to screening). Please refer to Section 6.1.2 and Appendix A • All patients: o A 52-week treatment period during which volanesorsen will be administered as a once weekly SC injection o Option to participate in an extended treatment period (up to an additional 52 weeks) o A 13-week post-treatment evaluation period or expanded access program The patients, Investigators, study staff, and the Sponsor will remain blinded to lipid data through the last patient's Week 13 visit of the open-label study or until results from the database locks for the ISIS 304801-CS6 and ISIS 304801-CS16 index studies becomes available, whichever comes first. Collection and measurement of race and ethnicity, vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), adverse events (AE), concomitant medication/procedure information, lipid panel, blood viscosity, volanesorsen plasma concentrations, immunogenicity (IM) testing, platelet aggregation, liver/spleen magnetic resonance imaging (MRI), ECGs, echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Dietary counseling will be repeated at intervals throughout the treatment and follow-up period and a daily food/drink diary will be completed for the week prior to each quarterly visit by each patient. Following the Week 52 visit, patients will have the option of participating in an expanded

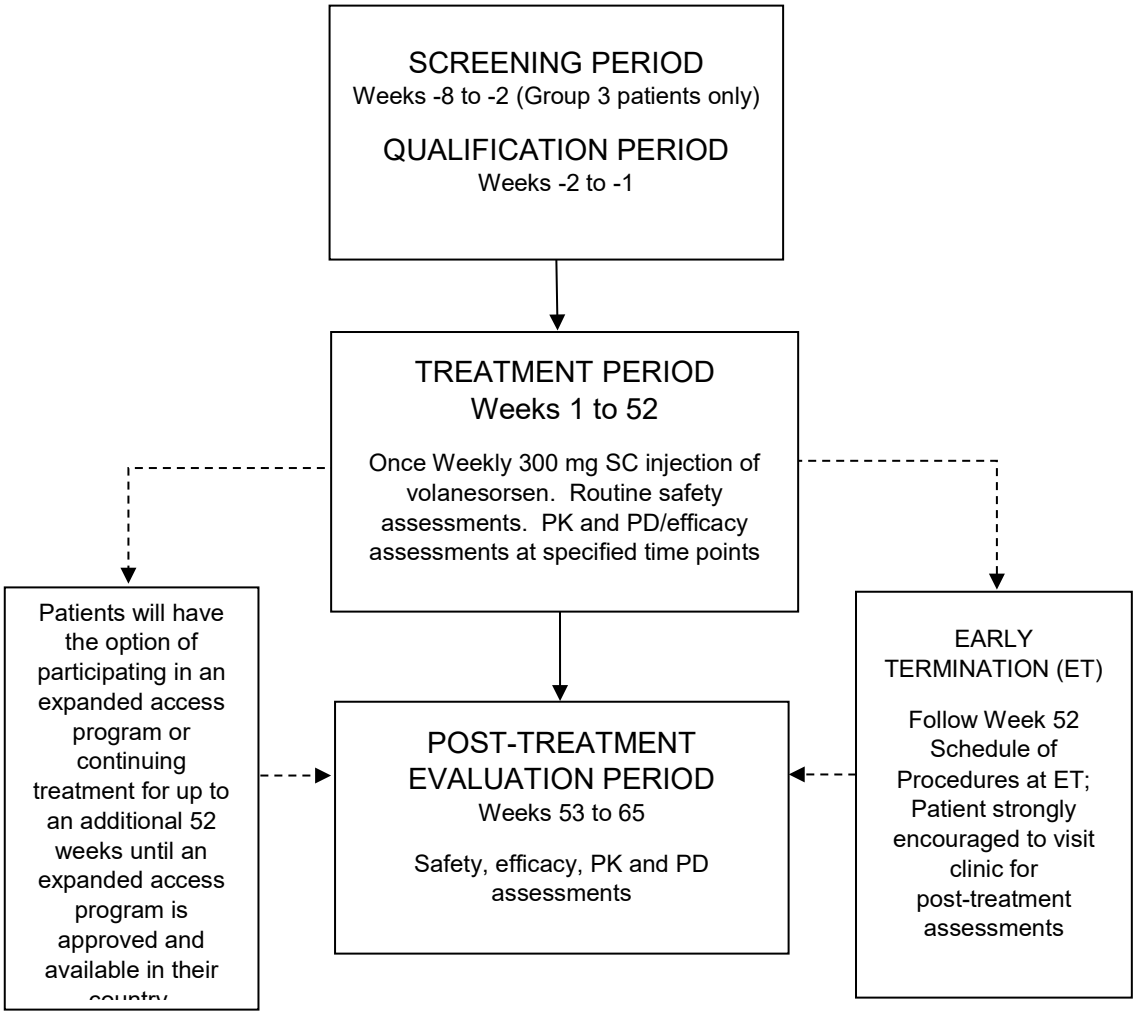
PROTOCOL SYNOPSIS *Continued*

	access program or continuing treatment for up to an additional 52 weeks until an expanded access program is approved and available in their country. Patients not participating in an expanded access program will enter the 13-week post-treatment evaluation period.
Safety and Tolerability Evaluations	Overall safety and tolerability of volanesorsen will be assessed by determining the incidence and severity of adverse and serious adverse events (including independently adjudicated events of acute pancreatitis and MACE), withdrawals due to adverse events, and changes in laboratory and other safety parameters.
Planned Analyses	Safety Endpoints: • Adverse events including adjudicated events of acute pancreatitis and MACE • Vital signs and weight • Physical examinations • Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis) • Echocardiography • Electrocardiograms (ECGs) • Use of concomitant medications • MRIs • Platelet aggregation (may be evaluated) Efficacy Endpoints: • Percent change and absolute change from baseline in fasting TG • Frequency and severity of patient reported abdominal pain during the treatment period • Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-high-density lipoprotein-cholesterol (non-HDL-C), apolipoprotein B [apoB], high-density lipoprotein-cholesterol (HDL-C), apolipoprotein A-1 [apoA-1], very-low-density lipoprotein-cholesterol (VLDL-C), and LDL-C • Percent change from baseline in fasting total apolipoprotein C-III (apoC-III) • Change in blood viscosity (may be evaluated) • Quality of Life questionnaires (EQ-5D, SF-36) • Adjudicated acute pancreatitis event rate • Other symptoms: eruptive xanthoma, lipemia retinalis
Pharmacokinetic Evaluations	Plasma samples will be taken from all patients for the measurement of volanesorsen as follows: trough levels (pre-dose) throughout treatment and post-treatment levels during the post-treatment follow-up period. In a subset of patients, more frequent assessment of plasma concentrations of volanesorsen will be performed to determine volanesorsen pharmacokinetic

PROTOCOL SYNOPSIS *Continued*

	parameters. Plasma sample collection time points are detailed in Appendix A and Appendix C.
Statistical Considerations	No sample size calculations were performed as this is an open-label study.
Sponsor	Akcea Therapeutics, Inc.
Collaborator	Ionis Pharmaceuticals, Inc.

STUDY DESIGN AND TREATMENT SCHEMA



STUDY GLOSSARY

Abbreviation/Acronym	Definition
ADA	anti-drug antibody
AE	adverse Event
ALP	alkaline Phosphatase
ALT	alanine Aminotransferase
ANA	antinuclear Antibody
apoA-1	apolipoprotein A-1
apoB	apolipoprotein B
apoC-III	apolipoprotein C-III
apoE	apolipoprotein E
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
CBC	complete blood count
C_{max}	maximum observed drug concentration
CRF	case report form
DNA	deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
ET	early termination
FAS	full analysis set
FCS	Familial Chylomicronemia Syndrome
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
GPIHBP1	glycosylphosphatidylinositol-anchored hdl-binding protein 1
HAPI	heritability and phenotype intervention
HbA1c	glycated hemoglobin
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein-cholesterol
hsCRP	High-sensitivity C-reactive protein
ICH	International Conference on Harmonization
IDL	intermediate density lipoprotein
IEC	Independent Ethics Committee

IM	immunogenicity
Index Studies	ISIS 304801-CS6 and ISIS 304801-CS16
INR	International Normalized Ratio
IRB	Institutional Review Board
IXRS	Interactive Voice/Web-Response System
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein-cholesterol
LMF1	lipase maturation factor 1
LPL	lipoprotein lipase
MACE	major acute cardiovascular event
MOE	2′-*O*-(2-methoxyethyl)
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NCS	not clinically-significant
NOAEL	no-observed-adverse-effect level
non-HDL-C	non-high-density lipoprotein-cholesterol
OTC	over the counter
PFS	prefilled syringe
PD	pharmacodynamic
PK	pharmacokinetic
PPS	per protocol set
PT	prothrombin time
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SUSAR	suspected unexpected serious adverse reaction
T2DM	type 2 diabetes mellitus
T_{max}	time to maximal concentration
TG	triglycerides
Treatment-emergent	occurring after first dose of Study Drug
TRL	triglyceride-rich lipoproteins
ULN	upper limit of normal
VLDL	very-low-density lipoprotein
VLDL-C	very-low-density lipoprotein-cholesterol
VLDL-TG	lipoprotein-triglyceride
WMA	World Medical Association

1. OBJECTIVES

The objective of the study is to evaluate the safety and efficacy of treatment and extended treatment with volanesorsen in patients with familial chylomicronemia syndrome.

2. BACKGROUND AND RATIONALE

2.1 Overview of Disease

Familial Chylomicronemia Syndrome (FCS) is an inherited disease characterized by severe hypertriglyceridemia and chylomicronemia, and risk or history of pancreatitis. It is a rare autosomal recessive disease that can be diagnosed either in childhood or adulthood.

Fasting plasma triglyceride (TG) levels in FCS patients are typically 10-fold to 100-fold above normal (1,500 to 15,000 mg/dL), despite extreme dietary fat restriction (20 g or approximately 15-20% of daily calorie intake) (Brunzell 1999-2011). Patients with FCS often present in infancy or childhood with frequent and severe abdominal pain, repetitive colicky pain, repeated episodes of potentially fatal acute pancreatitis, and failure to thrive (Brunzell 1999-2011; Tremblay et al. 2011). Physical examination frequently reveals eruptive xanthomas, lipemia retinalis and hepatosplenomegaly, and plasma from patients appears lactescent, interfering with determination of other laboratory parameters (Tremblay et al. 2011).

Patients with fasting triglyceride levels > 10 mmol/L probably have a component of chylomicronemia. Clinical diagnosis would include evidence of clinical features of chylomicronemia syndrome and secondary causes such as uncontrolled type 1 or type 2 diabetes mellitus (T2DM), hypothyroidism, poor diet, alcohol use, nephrotic syndrome or use of associated medications should be ruled out. The diagnosis of FCS may be made more specifically by genotyping or confirmation of very low or absent lipoprotein lipase (LPL) enzyme activity in post heparin plasma (Brunzell 1999-2011).

Patients with FCS carry a heavy burden of medical complications, the most serious, as described above, being an extreme risk of recurrent and potentially fatal pancreatitis. Due to the recurrent episodes of acute pancreatitis, these patients may also develop chronic pancreatitis and signs of exocrine or endocrine pancreatic insufficiency, including diabetes mellitus (Gaudet et al. 2013). While the pathophysiology underlying chylomicron-related pancreatitis has not been completely elucidated, 1 hypothesis is that large chylomicrons lodged in pancreatic capillaries are exposed to pancreatic lipase, with the subsequent release of free fatty acids through the hydrolysis of chylomicron-associated TGs. High concentrations of free fatty acids are thought to damage pancreatic cells leading to emergent pancreatitis (Yang et al. 2009; Berglund et al. 2012).

The etiology of extreme hypertriglyceridemia in FCS is considered to be ineffective triglyceride clearance, due to an extremely low level of LPL activity. LPL normally functions to hydrolyze triglycerides (TG) in chylomicrons along the luminal surface of capillaries, mainly in heart, skeletal muscle, and adipose tissue, promoting triglyceride clearance from the circulation. LPL is regulated by a number of key genes, and loss-of-function mutations in one of these genes, or the LPL gene itself, results in FCS (Surendran et al. 2012). In addition to loss of function mutations, null mutations, and nonsense mutations in the LPL gene, other genes currently identified in FCS patients, and known to directly influence LPL activity include: apolipoprotein C-II (APOC2) a cofactor for LPL (Schuster et al. 2011); apolipoprotein A-V (APOA5) an enhancer of LPL activity (Schaap et al. 2004); lipase maturation Factor 1

(LMF1), a transmembrane protein involved in LPL maturation (Doolittle et al. 2009); glycosylphosphatidylinositol-anchored HDL-binding protein 1 (GPIHBP1), a capillary endothelial cell protein that provides a platform for LPL-mediated processing of chylomicrons (Beigneux et al. 2007).

2.2 Therapeutic Rationale

Apolipoprotein C-III (ApoC-III), a key regulator of plasma triglyceride levels, is a 79 amino acid glycoprotein synthesized principally in the liver (Ooi et al. 2008; Figure 1). ApoC-III is a major regulator of lipoprotein metabolism and plays a pivotal role in regulating plasma TG levels (Chan et al. 2008). It is a component of triglyceride-rich lipoproteins (TRLs) and a potent inhibitor of LPL (Lemieux et al. 2003). At higher concentrations apoC-III also inhibits hepatic lipase activity (Kinnunen and Ehnolm 1976), an enzyme which plays an important role in the conversion of dense very-low-density lipoprotein (VLDL) to intermediate density lipoprotein (IDL) and to LDL (Mendivil et al. 2010), as well as in the remodeling of HDL (Brown et al. 2010). In addition, increased apoC-III content adversely affects apoE-mediated hepatic uptake of TG-rich remnants (Mann et al. 1997). Thus, elevated plasma apoC-III levels are associated with impaired hydrolysis and retarded clearance of TG-rich particles, resulting in the accumulation of lipoprotein-triglyceride (VLDL-TG) and chylomicrons in plasma and the development of hypertriglyceridemia (Ito et al. 1990).

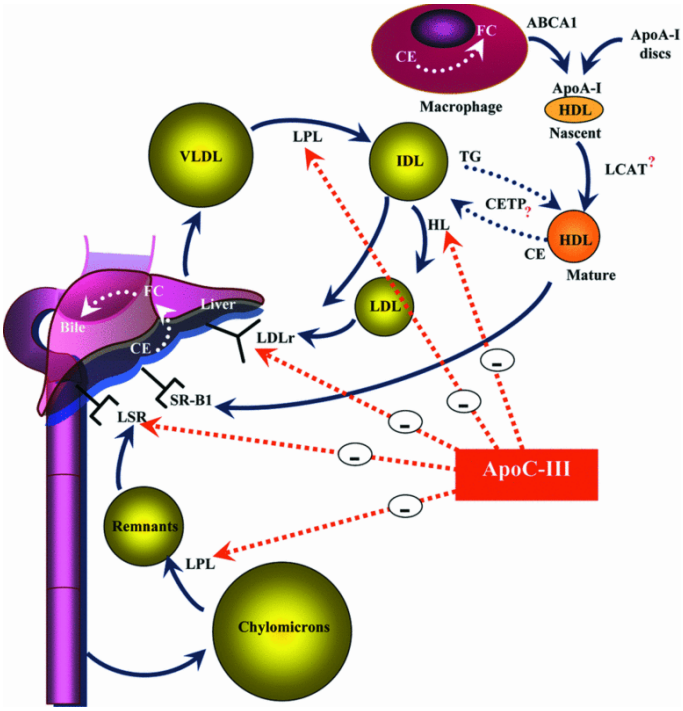


Figure 1 ApoC-III Regulates Lipoprotein Metabolism by Multiple Mechanisms

From Ooi et al. 2008; ABCA1 = ATP-binding cassette A1, apo = apolipoprotein, CE = cholesterol ester, CETP = cholesterol ester transfer protein, FC = free cholesterol, HDL = high-density lipoprotein, HL = hepatic lipase, IDL = intermediate-density lipoprotein, LCAT = lecithin cholesterol acyltransferase, LDL = low-density lipoprotein, LDLr = LDL receptor, LPL = lipoprotein lipase, LSR = lipolysis-stimulated receptor, SR-B1 = scavenger receptor B-1, TG = triglyceride, VLDL = very low-density lipoprotein.

Mechanistically, FCS is primarily a consequence of ineffective clearance of TRL. ApoC-III is a prominent component of TRL (e.g., VLDL and chylomicrons). In addition to its role in inhibiting LPL, apoC-III inhibits TRL remnant (TG-depleted remnant lipoprotein) uptake by hepatic lipoprotein receptors by steric inhibition of the interaction of apoE with these receptors.

Human genetic data have demonstrated positive phenotypic associations with loss (e.g., null or nonsense mutations) and negative effects with gain of function mutations (Atzmon et al. 2006; Pollin et al. 2008; Petersen et al. 2010). A novel nonsense mutation in the apoC-III gene was identified in the heritability and phenotype intervention (HAPI) heart study in Old Order Amish that results in lower plasma apoC-III and TG levels and lower LDL-C, increased HDL-C and reduced atherosclerosis (Pollin et al. 2008). In another study involving a group of 214 Ashkenazi Jews of advanced age (had passed or nearly reached 100 years of age), genotype analysis revealed a polymorphism in the apoC-III gene (APOC3-641CC genotype) with a clear pattern of age-dependent frequency that was associated with significantly lower levels of apoC-III protein, a favorable lipoprotein profile and increased longevity (Atzmon et al. 2006). In contrast to the Amish and Ashkenazi apoC-III polymorphisms associated with lower plasma TG, apoC-III polymorphisms associated with higher plasma TG have also been recently described (Petersen et al. 2010). In a cohort of lean (mean body mass index [BMI] = 24.7 ± 3.6 kg/m^2) Asian Indians, carriers of apoC-III variant alleles (C-482T, T-455C, or both) were noted to have significantly higher plasma apoC-III and TG levels, and decreased ability to clear postprandial plasma TG from the circulation. Taken together, the available data strongly support the development of a therapy that reduces plasma apoC-III levels in order to reduce the very high circulating triglyceride and chylomicron levels that are accompanied by increasing risk for acute pancreatitis.

Given the profound reductions in TGs observed with volanesorsen treatment in FCS patients who have no detectable LPL activity (See Section 2.3.4), and the mechanistic data available to date on apoC-III function, potential mechanisms that explain how apoC-III inhibition results in triglyceride reduction in FCS patients include: (1) enhancing the very small residual amounts of LPL activity that these patients may have, below the limit of detection of the assay in many cases (2) potentially enhanced activity of other lipases also involved in the metabolism and breakdown of TGs, such as hepatic lipase or endothelial lipase (Kinnunen and Ehnolm 1976), and (3) apoC-III interaction with Apolipoprotein E (apoE), an important factor in liver reuptake of lipid particles by blocking apoE-mediated uptake of lipid particles in the liver (Breyer et al. 1999), and therefore, reducing apoC-III might enhance apoE-mediated uptake of lipid particles. Volanesorsen-mediated reduction of apoC-III could be contributing to one or all of these mechanisms resulting in the observed potent and sustained reductions in TG.

Through a novel apoC-III lowering mechanism of action, volanesorsen may provide the potential to manage triglyceride levels in FCS patients.

2.3 Volanesorsen

2.3.1 Mechanism of Action

Volanesorsen is a second-generation antisense oligonucleotide (ASO) drug targeted to human apoC-III. It is complementary to a region within the 3' untranslated region of the apoC-III messenger ribonucleic acid (mRNA) and binds to the mRNA by Watson and Crick base pairing. The hybridization (binding) of volanesorsen to the cognate mRNA, results in the RNase H1-mediated degradation of the apoC-III

mRNA, thus preventing production of the apoC-III protein. Maximal antisense-mediated reduction of target mRNA levels is typically greater than 90% of control levels in sensitive tissues (Crooke and Bennett 1996; Zhang et al. 2010). Furthermore, reduction in target mRNA levels using this approach correlates directly with a subsequent reduction in target protein levels.

2.3.2 Chemistry

Chemically, volanesorsen is a synthetic oligomer of 20 nucleotides (i.e., a 20-mer) that are connected sequentially by phosphorothioate linkages. The nucleotide sequence of volanesorsen (Figure 2) is complementary to a 20-nucleotide stretch within the 3' untranslated region of the apoC-III mRNA transcript at base position 489-508. Structurally, the oligonucleotide has 3 regions. Two (2) of them, the 5 nucleotides at the 5' end and the 5 nucleotides at the 3' end, are composed of 2'-*O*-(2-methoxyethyl) (MOE)-modified ribonucleotides. These MOE-modified nucleotides confer (1) increased affinity to the target mRNA (Altmann et al. 1996; McKay et al. 1999), (2) increased resistance to exonucleases and endonucleases (thereby increasing stability in tissue) (Geary et al. 2003), and (3) amelioration of some of the high dose toxicities thereby resulting in an improved safety profile compared to first generation antisense drugs containing phosphorothioate modified oligodeoxynucleotides (DNA) (Henry et al. 2000). The third region, the central portion of the oligonucleotide, is composed of 10 oligodeoxynucleotides. This chimeric design is called a MOE-Gapmer, and volanesorsen employs this chimeric structure to enable use of the RNase H1-mechanism for antisense activity. This is because while the 2'-MOE modification confers increased stability and affinity, it does not support RNase H1 catalysis of RNA hybridized to 2'-MOE-modified nucleotides (McKay et al. 1999). This is caused by conformational changes induced in the heteroduplex by 2'-alkoxy:RNA hybrids that are not recognized by RNase H1 enzymes (Inoue et al. 1987; Monia et al. 1993). By limiting the 2'-MOE modification to nucleotides flanking the phosphorothioate oligodeoxynucleotide core, the beneficial attributes of the 2'-MOE chemistry are preserved while also retaining RNase H1 recognition.

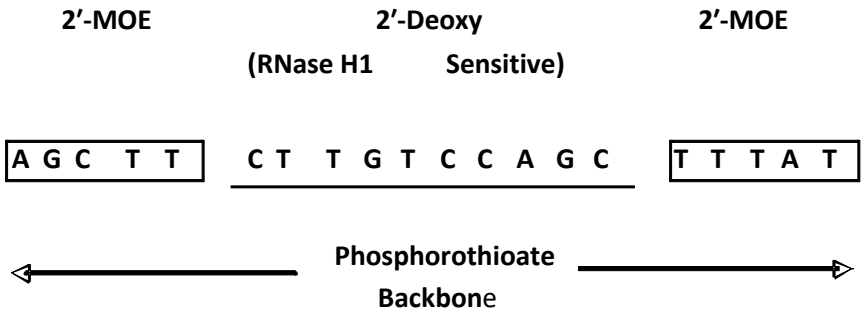


Figure 2 Design of Chimeric 2'-MOE Phosphorothioate Oligonucleotides (MOE-Gapmer). The sequence of volanesorsen is shown

2.3.3 Preclinical Experience

Inhibition of apoC-III using volanesorsen has been shown to potently reduce hepatic apoC-III mRNA as well as plasma apoC-III protein and TG in a dose- and time-dependent fashion in several species,

including human apoC-III transgenic mice, and other rodent and monkey models. Treatment with volanesorsen also resulted in reduced VLDL and chylomicron TG and reduced postprandial TG in hypertriglyceridemic monkeys (Graham et al. 2013).

The pharmacokinetics (PK) and toxicity of volanesorsen have been assessed in mice, rats, and cynomolgus monkeys. General toxicity studies with volanesorsen for up to 39 weeks of treatment followed by up to a 20-week recovery period are complete. The preclinical toxicology program for volanesorsen consists of single dose safety pharmacology studies in the monkey (cardiovascular) and mouse (neurobehavioral and pulmonary assessment studies), *in vitro* and *in vivo* genetic toxicity assessment, repeat dose fertility and/or developmental reproductive toxicology studies in the mouse and rabbit and evaluation in the *in vitro* human
Ether-á-go-go-related gene (hERG) assay.

Volanesorsen treatment-related findings in mice and monkeys were generally consistent with those expected for the 2'-MOE-class of ASOs. Treatment-related findings included effects consistent with drug accumulation in tissues in rodents and monkeys, species-dependent proinflammatory response in rodents and monkeys and complement activation and reductions in platelet counts in the monkey. In the mouse and monkey general toxicity studies, reduction of hepatic apoC-III mRNA (> 75%) was not associated with any findings that could be considered related to the pharmacologic inhibition of apoC-III for up to 39 weeks of treatment.

The long-term, chronic toxicology studies in rodents with volanesorsen produced a significant proinflammatory response that led to subsequent effects on the heart at high doses. The rodent species are most sensitive to the proinflammatory effects of antisense molecules. Importantly, these effects on the heart were not observed in the monkey chronic toxicity studies even at the highest doses tested where drug exposure was higher than that in rodents.

Because these changes were not observed in monkeys, the findings in the heart are considered to be rodent-specific and not relevant to humans. Nevertheless, such effects will be monitored by measurement of echocardiograms that will be included in this clinical study.

Volanesorsen caused no untoward effects in safety pharmacology studies (*in vitro* and *in vivo*) and was non-genotoxic (*in vitro* and *in vivo*). Volanesorsen had no effects on fertility or embryo/fetal development in the mouse or rabbit reproductive toxicity studies. In these studies, volanesorsen was detected in placental tissue but not in fetal tissue indicating that little, if any, drug was able to cross the placenta to reach the fetus. Reduction of apoC-III mRNA (64% in males and 47% in females) also did not affect fertility or cause untoward effects on embryo/fetal development in mice.

Detailed information concerning the preclinical studies conducted with volanesorsen can be found in the volanesorsen Investigator's Brochure.

2.3.4 Clinical Experience

Detailed information concerning the clinical studies conducted with volanesorsen can be found in the volanesorsen Investigator's Brochure. A summary is included below.

The clinical experience with volanesorsen includes clinical trials in healthy subjects, patients with hypertriglyceridemia, FCS, or familial partial lipodystrophy. Overall, 431 patients and healthy volunteers

have taken part in the clinical development program, of whom 325 have received at least 1 dose of volanesorsen. Ninety-five (95) patients with FCS have been enrolled in studies, all showing clinically meaningful reductions in plasma triglyceride. Patients with FCS continue on treatment in the open-label extension (OLE) and triglyceride reductions persist at similar levels as reported in earlier studies.

In the completed Phase 1 and Phase 2 studies, volanesorsen was well-tolerated and demonstrated a favorable safety profile. There was no clinical or laboratory evidence of drug-drug interactions despite many patients in the Phase 2 clinical trials receiving concomitant medications that are known to be associated with elevations in hepatic enzymes, such as fibrates and statins. There were no volanesorsen-associated laboratory abnormalities suggestive of an effect on the renal (serum creatinine, proteinuria) or hepatic systems (alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin). There was a reduction (mean reduction < 30%) in platelets in volanesorsen vs. placebo with mean nadirs for all doses remaining above the lower limit of normal (LLN). The most frequently reported adverse events (AEs) were mild, non-progressive events at the injection site. In Phase 2, a single serious adverse event (SAE) of secondary serum sickness-like reaction was reported as related to Study Drug. All clinical trials of volanesorsen have shown large and clinically meaningful reductions in fasting plasma apoC-III and TG (~80% and 70%, respectively, mean reduction from baseline with 300 mg dose) with a very high degree of consistency of response between the different patient groups. This includes healthy volunteers, patients with moderate to severe hypertriglyceridemia not on background TG-lowering therapy, patients with moderate to severe hypertriglyceridemia on a background stable fibrate therapy (Gaudet et al. 2015), patients with FCS, and patients with T2DM.

In a Phase 2 study, 3 patients with FCS were treated with 300 mg/wk volanesorsen in an open-label fashion. These patients had a mean baseline fasting TG level of 1,844 mg/dL and all 3 patients achieved TG levels below or close to 500 mg/dL during the treatment period out to Day 92 (Figure 3). Two (2) of the FCS patients had an absolute reduction in fasting TG in excess of 1,500 mg/dL (Gaudet et al. 2014).

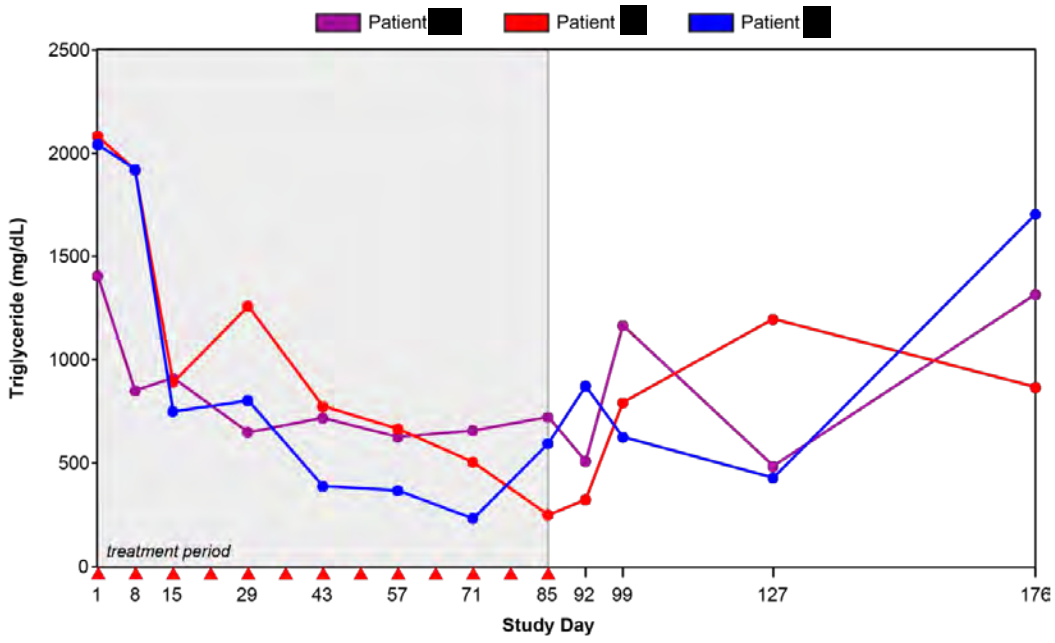


Figure 3 Fasting Triglycerides in Patients with FCS Treated with Volanesorsen

In the completed pooled Phase 3 studies (ISIS 304801-CS6 (hereafter referred to as CS6) and ISIS 304801-CS16 (hereafter referred to as CS16), the most common AEs associated with volanesorsen administration were tolerability at the injection site and platelet reductions. The majority of the injection site AEs were mild, none were severe, and the incidence appeared to decrease over time. No deaths have been associated with volanesorsen treatment to date. No cardiac toxicity was associated with volanesorsen treatment. There were no abnormal QTc findings and no study-drug related adjudicated major adverse cardiac events (MACE). There is no evident association between volanesorsen treatment and changes in renal or liver functions.

The safety profile of volanesorsen has been well-described in this development program, which has identified 3 safety risks: thrombocytopenia (an identified risk), constitutional symptoms (flu-like reactions and influenza-like illness), and injection site reactions (a tolerability signal). Spontaneous, mild-to-severe thrombocytopenia has been described in the FCS patient population (Gaudet et al. 2017) but is increased by treatment with volanesorsen. Less frequent and less pronounced platelet declines were also observed with volanesorsen treatment in the hypertriglyceridemic (HTG) population of CS16. When fully complied with, frequent monitoring for this effect and appropriate dose adjustments have been successful both in preventing and promptly detecting the occurrence of severe platelet declines and often in retaining patients on treatment.

2.4 Rationale for Dose and Schedule of Administration

The dose and schedule selected for this study is 300 mg per week for 52 weeks. The dose of 300 mg per week and dose reduction to 300 mg every 2 weeks (delivered as either a single 300 mg dose or as 150 mg once-weekly, respectively) are supported by both the cumulative nonclinical data available to date and the Phase 2 and 3 clinical data. In nonclinical studies, volanesorsen treatment-related effects in rodents and monkeys were consistent with drug accumulation in tissues and also include species-specific proinflammatory responses. In the monkey, the No-Observed-Adverse-Effect Level (NOAEL) was defined by the cumulative clinical pathology results and histopathology data which provide an adequate clinical margin. Nonclinical findings were not considered to be related to the pharmacologic inhibition of apoC-III.

The safety data to date suggest that volanesorsen has been well-tolerated at dose levels up to 300 mg in patients with high triglycerides (including type 2 diabetes patients and administration in combination with fibrates and statins) with the most common AEs being local to the injection site and predominantly mild. A pooled analysis of safety for the Phase 2 studies did not demonstrate any clear difference in safety or tolerability between the different doses tested (100 mg, 200 mg, and 300 mg per week for 13 weeks).

Analysis of the cohorts in which volanesorsen was studied at different doses demonstrates dose-dependent pharmacology with respect to pharmacodynamic (PD) effect on the target, apoC-III, with a clear difference in the TG-lowering effect between the different doses in the 100 mg to 300 mg dose range as compared to placebo.

In addition to the nonclinical and clinical experience of volanesorsen, the dose and schedule of administration is supported by the preclinical and clinical safety experience of several other 2'-MOE-

modified ASOs that have been administered intravenously and subcutaneously in multiple clinical studies at doses up to 1200 mg and for treatment durations that exceed 24 months (Santos et al. 2015).

3. EXPERIMENTAL PLAN

3.1 Study Design

This is an open-label study of:

Group 1: ISIS 304801-CS6 (index study) roll-over FCS patients

Group 2: ISIS 304801-CS16 (index study) roll-over FCS patients

Group 3: FCS patients who did not participate in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies

Up to approximately 70 patients will receive 300 mg once weekly volanesorsen for 52 weeks.

Following the Week 52 visit, patients will have the option of participating in an expanded access program or continuing treatment for up to an additional 52 weeks until an expanded access program is approved and available in their country. Patients not participating in an expanded access program will enter a 13-week post-treatment evaluation period.

3.2 Number of Study Centers

This study will be conducted at multiple centers worldwide.

3.3 Number of Patients

Up to approximately 70 patients will be dosed.

3.4 Overall Study Duration and Follow-up

The Study will consist of the following periods:

3.4.1 Group 1 and 2 Patients (participated in ISIS 304801-CS6 or ISIS 304801–CS16 index study): Qualification

A period of up to 2 weeks (unless approved by the Sponsor) is given to complete qualification assessments outlined in the Schedule of Procedures. Please refer to Section 4.1 and Appendix A.

3.4.2 Group 3 Patients (did not participate in an index study): Screening/Qualification

An up to 8-week screening and qualification period, including a diet stabilization period of at least 6 weeks (screening and diet stabilization period may be reduced, per Sponsor approval, if the patient is following a diet for optimal control of TGs and disease management prior to screening. Please refer to Section 6.1.2 and Appendix A.

3.4.3 Treatment

The treatment period is 52 weeks. Eligible patients will report to the Study Center for assessments at specified intervals throughout the 52-week treatment period as detailed in the Schedule of Procedures

(Appendix A). During the treatment period, volanesorsen is administered by SC injection once weekly.treatmenttreatment

3.4.4 Post-Treatment

Patients not participating in the extended treatment period will enter the post-treatment evaluation period of 13 weeks, consisting of 7 Study Center visits on Weeks 53, 54, 55, 56, 57, 58, and 65 (Weeks 53, 54, 55, 56, 57, and 58 may be conducted by a home healthcare nurse). Patients who complete, or terminate early from, the extended treatment period without subsequently participating in an expanded access program will enter a 13-week post-treatment evaluation period consisting of 7 Study Center visits on Weeks 105, 106, 107, 108, 109, and 110 (which may be conducted by a home healthcare nurse), and Week 117 (Appendix A).

3.5 End-of-Study

The End-of-Study is last patient, last visit.

3.6 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will review (as needed) safety, tolerability and efficacy data collected on volanesorsen during this study. Based on its ongoing assessment of the safety and tolerability of volanesorsen, the DSMB will provide recommendations to the Sponsor for modifying, stopping or continuing the study as planned. Details on the safety assessments, frequency of review and meeting schedules are outlined in the DSMB Charter and/or the statistical analysis plan (SAP).

4. PATIENT ENROLLMENT

4.1 Screening/Qualification

Before patients may be enrolled into the study, the Sponsor requires a copy of the Study Center's written independent ethics committee/institutional review board (IEC/IRB) approval of the protocol, informed consent form, and all other patient information.

Patients or their legally acceptable representatives must sign the consent form before any study-specific procedures or evaluations related to this open-label study are performed.

Groups 1 and 2 (Qualification): During the qualification period, the eligibility of the patient to enroll in the open-label study will be determined. Final assessments from the ISIS 304801-CS6 or ISIS 304801-CS16 studies may be used for qualification. A period of up to 2 weeks after completion of the ISIS 304801-CS6 or ISIS 304801-CS16 index studies (unless approved by the Sponsor) is given to complete qualification. Qualified patients will retain the unique patient identification number that was assigned to them during the ISIS 304801-CS6 or ISIS 304801-CS16 index studies. The patient identification number will be used to identify the patient throughout the extension trial and must be used on all study documentation related to that patient. The patient identification number must remain constant throughout the extension trial.

Group 3 (Screening and Qualification): At the time of consent, the patient will be considered enrolled into the study and will be assigned a unique screening number before any study procedures, including

screening procedures, are performed. At the time of enrollment, patients will be assigned a unique patient identification number. This number will be used to identify the patient throughout the trial and must be used on all study documentation related to that patient. The screening number and patient identification number must remain constant throughout the entire trial. In the event the patient is re-consented and re-screened the patient must be given a new screening number. Screening numbers and patient identification numbers, once assigned, will not be re-used.

4.2 Enrollment

Patients will be enrolled into the treatment phase of the study after all Screening (Group3) and qualification assessments have been completed and after the Investigator has verified that they are eligible per criteria in Sections 5.1 and 5.2. No patient may begin treatment prior to enrollment.

Eligible patients will be enrolled using an Interactive Voice/Web-Response System (IXRS).

5. PATIENT ELIGIBILITY

To be eligible to participate in this study candidates must meet the following eligibility criteria within 2 weeks of Study Day 1, or at the time point specified in the individual eligibility criterion listed.

5.1 Inclusion Criteria

1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law
2. Age ≥ 18 years at time of informed consent
3. Groups 1 and 2: Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement.

   Groups 2 and 3: Patients must also meet the following criteria in order to enter into the open-label Study:

   a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L)

   b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) supported by documentation of at least 1 of the following:

      - Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1)
      - Post heparin plasma LPL activity of ≤ 20% of normal in medical history. Note: testing of LPL activity should not be performed to confirm eligibility for the study

   c. Group 2: Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 index study

      Group 3: Fasting TG ≥ 750 mg/dL at Screening for this open-label study
4. Able and willing to participate in a 65-week study

5. Satisfy 1 of the following:

   a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved), abstinent*, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration.

   b. Males: Surgically sterile, abstinent* or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration.

   * Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception

5.2 Exclusion Criteria for Group 1 (ISIS 304801-CS6) and Group 2 (ISIS 304801-CS16) Index Study Roll-over Patients

1. Have any new condition or worsening of existing condition which in the opinion of the Investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study.
2. Unwilling to comply with lifestyle requirements for the duration of the study (Section 6.3).

Exclusion Criteria for Group 3 (patients who did not participate in an index study)

1. Diabetes mellitus with any of the following:
   a. Newly diagnosed within 12 weeks of screening
   b. HbA1c ≥ 9.0% at Screening
   c. Recent change in anti-diabetic pharmacotherapy (change in dosage or addition of new medication within 12 weeks of screening [with the exception of ± 10 units of insulin])
   d. Anticipated need to change dose or type of medication during the treatment period of the Study (with the exception of ± 10 units of insulin)
   e. Current use of GLP-1 agonists
2. Severe hypertriglyceridemia other than due to familial chylomicronemia syndrome
3. Active pancreatitis within 4 weeks prior to screening

4. History within 6 months of screening of acute or unstable cardiac ischemia (myocardial infarction, acute coronary syndrome, new onset angina), stroke, transient ischemic attack or unstable congestive cardiac failure requiring a change in medication or major surgery within 3 months of screening

5. Any of the following laboratory values at Screening

    a. Hepatic:

        - Total bilirubin > upper limit of normal (ULN), unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL
        - ALT > 2.0 x ULN
        - AST > 2.0 x ULN

    b. Renal:

        - Persistently positive (2 out of 3 consecutive tests ≥ 1+) for protein on urine dipstick. In the event of a positive test eligibility may be confirmed by a quantitative total urine protein measurement of < 500 mg/24 hrs
        - Persistently positive (2 out of 3 consecutive tests ≥ trace positive) for blood on urine dipstick. In the event of a positive test eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field
        - Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault < 50 mL/min (MDRD or CKD-EPI formulas can be used instead of Cockcroft-Gault for estimation of GFR in patients with low body weight after discussion with Sponsor Medical Monitor)

    c. Platelet count < LLN for the central laboratory (i.e., < 140,000/mm^3)

    d. Cardiac Troponin I > ULN at Screening

    e. LDL-C > 130 mg/dL at Screening

    f. Any other laboratory abnormalities which, in the opinion of the Investigator or the Sponsor, would make the patient unsuitable for inclusion

6. Uncontrolled hypertension (BP > 160/100 mm Hg)

7. History of bleeding diathesis or coagulopathy or clinically-significant abnormality in coagulation parameters at Screening

8. History of heart failure with NYHA greater than Class II

9. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1

10. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B
11. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated
12. Treatment with another investigational drug, biological agent, or device within 1-month of screening, or 5 half-lives of investigational agent, whichever is longer
13. Unwilling to comply with lifestyle requirements (Section 6.3)
14. Use of any of the following:
    a. Statins, omega-3 fatty acids (prescription and OTC), or fibrates unless on a stable dose for at least 3 months prior to screening and dose and regimen expected to remain constant during the treatment period. Patients taking OTC omega-3 fatty acids should make every effort to remain on the same brand throughout the study
    b. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to screening
    c. Systemic corticosteroids or anabolic steroids within 6 weeks prior to screening unless approved by the Sponsor Medical Monitor
    d. Atypical antipsychotic medications (e.g., olanzapine and clozapine) unless on a stable dose for at least 3 months prior to screening and dose and regimen expected to remain stable throughout the study
    e. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to screening and dose and regimen expected to remain constant during the treatment period
    f. Glybera gene therapy within 2 years prior to screening
    g. Oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, and apixaban) unless on a stable dose for at least 4 weeks prior to screening and regular clinical monitoring is performed
    h. Tamoxifen, estrogens or progestins unless on a stable dose for at least 4 months prior to screening and dose and regimen expected to remain constant during the treatment period
    i. Plasma apheresis within 4 weeks prior to screening or planned during the study
    j. Prior exposure to ISIS 304801
    k. Any other medication unless stable at least 4 weeks prior to screening (Occasional or intermittent use of over-the-counter medications will be allowed at Investigator's discretion)
15. Blood donation of 50 to 499 mL within 30 days of screening or of > 499 mL within 60 days of screening
16. Known hypersensitivity to any of the excipients of the Study Drug (ISIS 304801 or placebo)

17. Have any other conditions, which, in the opinion of the Investigator or the Sponsor would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the study

6. STUDY PROCEDURES

6.1 Study Schedule

All required study procedures are outlined in Appendices A, B, C, and D.

6.1.1 Qualification (Groups 1 and 2)

Please refer to Section 4.1 and Appendix A.

6.1.2 Screening and Qualification (Group 3)

Before any study-specific procedures or evaluations are initiated, patients must sign and date the informed consent form. An 8-week period, including a diet stabilization period of at least 6 weeks (screening and diet stabilization period may be reduced, per Sponsor approval, if the patient is following a diet for optimal control of TGs and disease management prior to screening) is given to perform the screening evaluations. The qualification assessments will be performed at Week -2 to -1, ideally after patient eligibility has been determined, and on Study Day 1. Abnormal screening results may be retested for review by the Study Medical Monitor for eligibility purposes

6.1.3 Treatment Period

The patients, Investigators, study staff, and the Sponsor will remain blinded to lipid data through the last patient's Week 13 visit of the open-label study or until results from the database locks for the ISIS 304801-CS6 and ISIS 304801-CS16 index studies become available, whichever comes first.

During the treatment period, patients will report to the study center for clinic visits a minimum of 5 times during Weeks 1-52 (see Schedule of Procedures in Appendix A). Study Drug will be administered once weekly unless the patient is on a biweekly treatment schedule for safety reasons (Section 8.1). Collection and measurement of race and ethnicity, vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), AEs, concomitant medication/procedure information, lipid panel, blood viscosity, volanesorsen plasma concentrations, immunogenicity (IM) testing, platelet aggregation, liver/spleen MRI, ECGs, echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Adverse events at the injection site should be collected as AEs. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period and all patients will complete a daily food diary for one week prior to their quarterly visit. All blood and urine samples should be collected prior to volanesorsen administration. Blood sampling at Weeks 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, and 51 may be conducted by a home healthcare nurse. Approval for study procedures to be conducted by a home healthcare nurse on other outpatient visit days will require prior approval by the Sponsor. Patients must be fasted prior to drawing all blood samples and samples drawn locally should also be sent to the central laboratory for analysis whenever possible. Treatment instructions and training will be provided to the patient where applicable.

All reasonable attempts should be made to ensure compliance with the visit schedule as outlined in Appendix A. However, in the event that a visit does not occur or is delayed, all subsequent visits should be calculated based on the time elapsed since Day 1 rather than from the date of the previous visit.

6.1.4 Extended Treatment Period

Patients will have the option of continuing treatment for up to an additional 52 weeks until an expanded access program is approved and available in their country.

During the extended treatment period, patients will report to the study center for clinic visits during Weeks 54-104 (see Schedule of Procedures in Appendix A). Study Drug will be administered once weekly unless the patient is on a biweekly treatment schedule for safety reasons (Section 8.1). Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), AEs, concomitant medication/procedure information, lipid panel, volanesorsen plasma concentrations, IM testing, ECGs, and physical examinations will be performed according to the Schedule of Procedures in Appendix A. Adverse events at the injection site should be collected as adverse events. Dietary counseling will be reinforced at intervals throughout the extended treatment period. All blood and urine samples should be collected prior to volanesorsen administration. Blood sampling at Weeks 53, 54, 55, 56, 57, 58, 59, 60, 61, 62,63, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, and 103 may be conducted by a home healthcare nurse. Approval for study procedures to be conducted by a home healthcare nurse on other outpatient visit days will require prior approval by the Sponsor. Patients must be fasted prior to drawing all blood samples and samples drawn locally should also be sent to the central laboratory for analysis whenever possible. Treatment instructions and training will be provided to the patient where applicable.

6.1.5 Pharmacokinetic (PK) Subgroup

A subgroup of patients will participate in an extended PK collection. Patients in this subgroup will have more frequent PK sampling over a 24-hour period following the first dose on Study Day 1 in order to evaluate the plasma PK parameters of volanesorsen. Patients in this subgroup will have an additional visit to the clinic, or by a home healthcare nurse, on Day 2 to collect a 24-hour post-dose blood draw after treatment on Day 1. The detailed PK sampling schedules are outlined in Appendix C.

Participation in the PK subgroup is optional for sites and patients, and consent may be withdrawn for the subgroup-specific procedures (e.g., multiple blood draws for PK) without being withdrawn from the study. If a patient withdraws consent from the subgroup procedures, he/she should remain on study and continue to follow all the non-subgroup assessments and procedures as outlined in Appendix A.

6.1.6 Post-Treatment Period

After completion of the Week 52 visit assessments, patients will have the option of participating in an expanded access program or continuing treatment for up to an additional 52 weeks until an expanded access program is approved and available in their country as described in Section 6.1.4. Patients not participating in an expanded access program will enter the 13-week post-treatment evaluation period. This 13-week post-treatment evaluation period consists of 7 Study Center visits on Weeks 53, 54, 55, 56, 57, and 58 (which may be conducted by a home healthcare nurse), and Week 65 as outlined in the Schedule of Procedures in Appendix A. Patients who complete, or terminate early from, the extended

treatment period without subsequently participating in an expanded access program will enter a 13-week post-treatment evaluation period consisting of 7 Study Center visits on Weeks 105, 106, 107, 108, 109, and 110 (which may be conducted by a home healthcare nurse), and Week 117 as outlined in the Schedule of Procedures in Appendix A.

6.2 Additional Study Assessments

6.2.1 Laboratory Assessments

Laboratory analyte samples will be collected throughout the study. A list of these analytes is contained in Appendix B.

Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1-week and the result must be reviewed by the Investigator and confirmed to be acceptable before treatment can continue. All platelet count results will be promptly reviewed by the Investigator to determine if the count has met a stopping rule, or the dose reduction rule of 100,000/mm^3, or the dose pause rule of 75,000/mm^3.

Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor.

Should a patient experience constitutional or flu-like symptoms after Study Drug administration, investigators may consider additional laboratory assessments. For example, plasma and serum samples may be drawn for complement (Total C3, C4, C5a and Bb), hsCRP and for cytokine analysis.

6.2.2 Physical Exams and Vital Signs

Physical exams and vital signs will be performed as indicated in the Schedule of Procedures (Appendix A). Vital signs should include weight, blood pressure, pulse rate, respiratory rate and body temperature. Blood pressure and pulse rate will be recorded after the patient has been in a sitting position for at least 5 minutes. Semi-supine systolic and diastolic blood pressure should always be measured on the same arm (preferentially on the left arm). Height will be measured at the Day 1 visit.

6.2.2.1 Eruptive Xanthoma

At each visit, patients will be asked whether they have had any episodes of eruptive xanthoma since their last visit and the number/duration of the events will be recorded. Physical exams should also include skin examination for presence/resolution of eruptive xanthomas. If a patient experiences an episode of eruptive xanthoma during the study, photos of the area should be taken, if possible.

6.2.2.2 Lipemia Retinalis

If possible, lipemia retinalis will be assessed by fundus photography prior to administration of the first dose of Study Drug (for ISIS 304801-CS16 roll-over patients) and repeated at Week 52. Images will be evaluated by an independent assessor, blinded to the patient's treatment assignment.

6.2.3 Echocardiography

Echocardiography for assessment of left and right ventricular function and mitral and aortic valve function will be conducted at Week 26 and Week 52 in all patients. For the purpose of assessment of treatment-emergent changes, all echocardiograms will be evaluated on an ongoing basis by an independent central reader. Results will be provided to the DSMB for their review.

6.2.4 ECG

The ECG will be recorded after the patient has been resting in a supine position for at least 5 minutes. ECGs will be performed in triplicate at Week 13, Week 26, Week 38, Week 52, and Week 65. Patients in the Extended Treatment Period will have ECGs performed in triplicate at Week 76 and Week 104.

6.2.5 MRI

MRI of the liver and spleen will be conducted at Week 52 for all patients for whom MRI is not contraindicated, e.g., patients having metal implants.

MRIs will be conducted using standardized procedures and settings. MRIs will be read by an independent central reader to assess liver fat and liver and spleen size**.**

6.2.6 Quality of Life Assessments

All patients will complete Quality of Life Questionnaires (EQ-5D and SF-36) at Week 1, Week 13, Week 26, Week 52, and Week 65.

6.2.7 Disease Symptom Diary

All patients will complete a symptom questionnaire once a week starting at the beginning of the qualification period and continuing to the end of the post-treatment follow-up period (Week 65).

6.2.8 Diet Monitoring

The diets of patients enrolled in the study will be monitored as follows:

1. All patients will be required to maintain a 7-day food diary prior to Week 1, Week 13, Week 26, Week 52, and Week 65.
2. Patients will receive diet/alcohol counseling by qualified study personnel at clinic visits throughout the course of the study. Qualified study personnel will telephone the patient to provide diet/alcohol counseling for visits that are conducted by a clinical service. Patients in the Extended Treatment Period will receive diet/alcohol counseling by qualified study personnel at clinic visits only.
3. In addition to the 7-day food diary and the diet /alcohol counseling during clinic visits, telephone calls from a dietitian or qualified study personnel to assess as to how each patient is maintaining their diet may be conducted randomly during the treatment and post treatment follow-up periods.

6.2.9 Family History

Family history of hypertriglyceridemia and pancreatitis will be collected for each patient.

6.2.10 Chart Review for Incidents of Acute Pancreatitis in Medical History (Group 2 and 3)

Patient records will be reviewed for incidents of acute pancreatitis occurring up to 5 years prior to screening and information relating to these events will be collected for independent adjudication.

6.3 Restriction on the Lifestyle of Patients

6.3.1 Contraception Requirements

All male patients and women of childbearing potential must refrain from sperm/egg donation and either be abstinent[†] or, if engaged in sexual relations of child-bearing potential, practice effective contraception from the time of signing the informed consent form until at least 13 weeks after their last dose of study treatment.

Male patients must also encourage their female partner to use effective contraception from the time of signing the informed consent until 13 weeks after the subject's last dose of study treatment.

For the purposes of this Study, women of childbearing potential are defined as any female who has experienced menarche, and who does not meet 1 of the following conditions:

- Postmenopausal: 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved
- 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Post hysterectomy

For the purposes of the study, effective contraception is defined as follows:

For male patients:

- Effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the use of condoms together with spermicidal foam/gel/film/ cream/suppository. Male patients must also encourage their female partner to use effective contraception from the time of signing the informed consent until 3 months after the patient's last dose of study treatment. Effective contraceptive for the female partner includes: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or barrier methods (female condom*, diaphragm, sponge, cervical cap) together with spermicidal foam/gel/film/cream/suppository. Male patients with partners that are pregnant must use condoms to ensure that the fetus is not exposed to the Study Drug.

For female patients:

- Using 1 or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or any 2 barrier methods (a combination of male or female condom* with diaphragm, sponge, or cervical cap) together with spermicidal foam/gel/film/cream/suppository.

* Note: A female condom and a male condom should not be used together as friction between the two can result in either product failing.

† Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception

6.3.2 Other Requirements

All patients will be required to fast for at least 10 hours and preferably not more than 12 hours before visits requiring fasted blood sampling.

All patients will be encouraged to follow a diet comprising ≤ 20 g fat per day during the study.

Alcohol should not be consumed during the study.

All patients will be given an instruction card that must be presented to the treating physician if a suspected case of pancreatitis occurs. The card will explain that the patient is in a clinical trial and that serum lipase and/or amylase measures should be done in order to adjudicate the event, based on Atlanta Classification (Banks et al. 2013). If serum or amylase activity is less than 3 x upper limit of normal (ULN), imaging, preferably contrast-enhanced computed tomography, should be considered to confirm the diagnosis of acute pancreatitis per the Atlanta Criteria.

7. STUDY DRUG

7.1 Volanesorsen Description

Volanesorsen drug product (ISIS 304801) characteristics are listed in Table 1.

Volanesorsen (ISIS 304801) is contained in glass prefilled syringes (PFS) or in glass vials. Volanesorsen and its storage and preparation instructions will be provided by the Sponsor or designee. Volanesorsen must be stored securely at 2 to 8°C and be protected from light.

Table 1 Volanesorsen (ISIS 304801) Characteristics

Study Drug	ISIS 304801 Prefilled Syringe	ISIS 304801 Vial
Strength	300 mg	200 mg
Volume / Formulation	1.5 mL 200 mg/mL ISIS 304801	1.0 mL 200 mg/mL ISIS 304801
Dose	300 mg / 1.5 mL	150 mg / 0.75 mL
Route of Administration	Subcutaneous injection	Subcutaneous injection

7.2 Packaging and Labeling

The Sponsor will provide the Investigator with packaged volanesorsen labeled (ISIS 304801) in accordance with specific country regulatory requirements.

7.3 Study Drug Accountability

The study staff is required to document the receipt, dispensing, and return/destruction of volanesorsen provided by the Sponsor. The Study Center must return all unused volanesorsen to the Sponsor or designee. All used syringes or vials must be disposed of as per the site's hazardous waste destruction policy.

8. TREATMENT OF PATIENTS

8.1 Volanesorsen Administration

For each individual patient, volanesorsen will be administered subcutaneously as a single 1.5 mL 300 mg injection once weekly for Weeks 1-52, and patients will continue to receive Study Drug as a single 300 mg/1.5 mL injection once-weekly for Weeks 53-104 of the study. Patients entering this ISIS 304801-CS7 study on a reduced dose or dose frequency of Study Drug (volanesorsen), for safety or tolerability reasons in their index study (ISIS 304801-CS6 or ISIS 304801-CS16), will receive a reduced dose or dose frequency of volanesorsen for continued safety or tolerability as outlined in Sections 8.5 and 8.6. Patients on dose reduction will receive either 300 mg/1.5 mL injections every 2 weeks or 150 mg/0.75 mL injections once-weekly. Treatment with a 150 mg dose during the study will use the glass vials containing 200 mg/mL of volanesorsen.

Patients should receive 1 dose per week, unless on a dose reduction of 300 mg every 2 weeks, with weeks always defined relative to Study Day 1. For example, if a patient receives the first dose on a Monday, subsequent doses should be given on Mondays, if possible. If a patient misses an injection, or if treatment on the usual day is not possible, the patient can reschedule the injection provided that 2 doses are administered at least 2 days apart.

Please refer to the Study Drug Manual provided by the Sponsor for more detailed instructions for volanesorsen preparation and administration.

8.2 Other Protocol-Required Drugs

There are no other protocol-required drugs.

8.3 Other Protocol-Required Treatment Procedures

There are no other protocol required treatment procedures for this study.

8.4 Treatment Precautions

There are no specific treatment precautions required for this study.

8.5 Safety Monitoring Rules

Please refer also to the 'Guidance for Investigator' section of the Investigator's Brochure.

For the purposes of safety monitoring, baseline is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 (e.g., qualification assessments or assessments from the final visits of ISIS 304801-CS6 and ISIS 304801-CS16 index studies if used for qualification).

In addition to the standard monitoring of clinical safety parameters, the following guidelines are provided for the monitoring of selected parameters chosen based on preclinical and clinical observations.

Confirmation Guidance: At any time during the study (Treatment or Post-Treatment Periods), the initial clinical laboratory results meeting the safety monitoring or stopping criteria presented below **must be confirmed** by performing measurements (ideally in the same laboratory that performed the initial measurement) on new specimens. All new specimen collections should take place as soon as possible (ideally within 3 days of the initial collection). For stopping rules, if the initial laboratory result is observed during the Treatment Period, the results from the retest **must be available** prior to administering the next dose of volanesorsen.

In addition to the safety monitoring parameters listed below, the Sponsor may request confirmation of additional lab values.

Re-treatment Guidance: Patients with initial laboratory test values that reach a stopping rule must not be re-dosed until the re-test results are available. In general, patients who do not meet the stopping rules based upon re-test may continue treatment. However, the Investigator and the Sponsor Medical Monitor (or appropriately qualified designee) should confer as to whether additional close monitoring of the patient is appropriate. Reduction in dose or dose frequency may also be initiated as noted in Section 8.7. If any of the stopping criteria described below (refer to Sections 8.6.1 to 8.6.3) are met, the patient will be dose paused or permanently discontinued (as described in the stopping criterion concerned) from further treatment with volanesorsen, and evaluated fully as outlined below and in consultation with the Sponsor Medical Monitor or appropriately qualified designee, and will be followed up in accordance with Section 8.8 of the protocol.

8.5.1 Safety Monitoring for Liver Chemistry Tests

The following rules are adapted from the draft guidance for industry, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," issued by the U.S. Department of Health and Human Services, Food and Drug Administration, July 2009. For a definition of Baseline please refer to guidance in Section 8.5 above.

In the event of an ALT or AST measurement that is > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) at any time during the study (Treatment or Post-Treatment Period), the initial measurement(s) should be confirmed as described above. Additional confirmatory measurements should also be performed if ALT or AST levels increase to 5 x ULN.

Frequency of Repeat Measurements: Patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) should have their liver chemistry tests (ALT, AST, alkaline phosphatase (ALP), international normalized ratio (INR) and total bilirubin) retested at least once-weekly until ALT and AST levels become ≤ 1.2 x ULN or 1.2 x baseline value if the baseline value was > ULN.

Further Investigation into Liver Chemistry Elevations: For patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), the following evaluations should be performed:

1. Obtain a more detailed history of symptoms and prior and concurrent diseases
2. Obtain further history for concomitant drug use (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
3. Obtain a history for exposure to environmental chemical agents and travel
4. Serology for viral hepatitis (HAV IgM, HBsAg, HCV antibody, CMV IgM, and EBV antibody panel)
5. Serology for autoimmune hepatitis (e.g., antinuclear antibody [ANA])

Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic CT or MRI scans, may be performed at the discretion of the Investigator, in consultation with the Sponsor Medical Monitor. Repetition of the above evaluations should be considered if a patient's ALT and/or AST levels reach 5 x ULN.

8.5.2 Safety Monitoring for Platelet Count Results

Actions to be taken in the event of reduced platelet count are shown in Table 3 in Section 8.6.3.

Monitor every 1 week unless otherwise specified. In addition, platelet function may be evaluated at any time during the study by aggregometry, using an approved point-of-care diagnostic device, in some patients. This additional functional testing may be performed at selected study centers.

Study Drug administration is contingent on the availability of the immediately preceding test result. An interpretable platelet value must be available within 7 days prior to treatment. Only the study doctor or qualified designee can authorize continued Study Drug administration based on an acceptable platelet value. Patients should not administer a dose until they have been contacted by their study doctor or designee and told that it is acceptable to dose. Authorization to dose must be documented in the patient's medical records.

Due to the 1 to 2-year study duration, it is anticipated that patients may undertake travel including vacations, which may impede weekly platelet monitoring. In some situations, it may be possible to arrange for local laboratory testing or use of the home healthcare service at their temporary location. The intent is to maintain weekly platelet monitoring and treatment where possible, as well as Investigator site contact with the study patients. However, if the above options are not possible, a temporary interruption of study treatment will be planned with a platelet count drawn within 3-5 days prior to departure and a prompt blood draw upon the patient's return which must be reported and reviewed by the Investigator prior to the patient resuming treatment.

Patients on dose pause should be monitored as per the platelet monitoring rules outlined in Section 8.8.1 until Study Drug administration is resumed.

The tests outlined in Table 2 should also be performed as soon as possible. Additional lab tests will be determined by the Sponsor Medical Monitor or designee in consultation with the Investigator.

Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor (See also Stopping Rules Section 8.6.3).

Table 2 Labs to Be Performed in the Event of a Platelet Count Less than the Lower Limit of Normal (x2) or < 100,000/mm^3 (x1)*

*In patients who have any 2 occurrences (consecutive or non-consecutive) of platelet count less than the lower limit of normal or who have any 1 occurrence of platelets < 100,000/mm^3. Labs only need to be performed once. Labs may be collected over multiple visits, if blood requirements are a concern, as per Investigator discretion.

Note: The following labs may change as additional data is assessed, and sites will be updated regarding any changes.

To Be Performed at Local Lab
Peripheral smear (should be performed locally, fixed and sent to central lab for review)
Fibrinogen split products or D-dimer on fresh blood
To Be Performed at Central Lab
Citrated sample for platelets
Coagulation panel (PT/INR, aPTT)
CBC with reticulocytes
Folate (folic acid)
Vitamin B12
Fibrinogen
von Willebrand factor
Total globulins, total IgA, IgG and IgM
Complement: total C3, total C4, Bb, C5a
hsCRP
Helicobacter pylori (breath test)
Serology for:
HBV, HCV, HIV (if not done recently for screening)
Rubella
CMV
EBV
Parvo B19
Auto-antibody screen:
Antiphospholipid
Rheumatoid factor
Anti-dsDNA
Anti-thyroid
To Be Performed at Specialty Lab(s)
Antiplatelet antibodies and Anti-PF4 assay
Anti-ASO antibody

8.5.3 Safety Monitoring for Minor Bleeding Events

Minor bleeding events are those that do not fulfill the criteria for major bleeding or clinically-relevant, non-major bleeding events (which are defined in Section 8.6.3), for example excess bruising, petechiae,

gingival bleeding on brushing teeth. If a minor bleeding event occurs, the Investigator must notify the Sponsor Medical Monitor and additional testing of coagulation parameters activated partial thromboplastin time (aPTT), prothrombin time (PT), INR and platelet count should be performed.

8.5.4 Safety Monitoring for Constitutional Symptoms

Patients will be instructed to promptly report any signs of symptoms of fever or constitutional symptoms that may arise during the study and the Investigator should closely evaluate all potential causes, including concomitant illness. Patients that experience persistent constitutional symptoms, should be discussed with the Sponsor Medical Monitor or designee to determine whether additional monitoring or laboratory tests are required.

Should a patient experience constitutional or flu-like symptoms after Study Drug administration, investigators may consider additional laboratory assessments. For example, plasma and serum samples may be drawn for complement (Total C3, C4, C5a and Bb), hsCRP, and for cytokine analysis.

8.5.5 Safety Monitoring for LDL-C Elevations

Beginning at Week 13, laboratory alerts will be in place to notify the Investigator if a patient has a low-density lipoprotein-cholesterol (LDL-C) > 160 mg/dL (> 130 mg/dL for patients with T2DM) on 2 consecutive visits. If this occurs, LDL-C values for this patient will be unblinded for the remainder of the study and the Investigator will be encouraged to initiate/adjust treatment to lower LDL-C according to country-specific guidelines (e.g., initiate statin therapy or increase the statin dose for patients who are already on treatment).

8.5.6 Safety Monitoring for Insulin, Oral Antidiabetic Medication and Glucose

All patients on insulin will monitor their glucose levels with a glucometer as per standard practice guidelines and bring their glucometer or glucometer log printout to every clinic visit. In addition, patients who are not on insulin but use a glucometer should also bring their glucometer and/or glucometer log printout to every clinic visit.

- The Investigator or delegate will review the glucometer reading or printout at every clinic visit to evaluate if fasting pre-breakfast self-monitored plasma glucose values exceed threshold values as per the Safety Monitoring Rules for Hyperglycemia below.

All diabetic patients will note any changes in their insulin dose and /or oral antidiabetic therapy, as well as any hypoglycemic episode they may experience.

- The Investigator or delegate will ask patients at every clinic visit if they made changes in their insulin dose or oral antidiabetic therapy, and if they experienced a hypoglycemic episode.
    - Patients will be instructed on the monitoring and management of hypoglycemic episodes at each visit.
    - Documented symptomatic hypoglycemic episodes should be captured as adverse events in the adverse event CRF. Documented symptomatic hypoglycemia is defined as typical hypoglycemia symptoms accompanied by measured plasma glucose ≤ 70 mg/dL (≤ 3.9 mmol/L).

- Any changes in insulin dose or oral antidiabetic therapy should be captured into the Concomitant Medication CRF.

8.5.7 Safety Monitoring for Documented Severe Hypoglycemia

A **documented severe hypoglycemic event** is defined as 1 in which the patient requires assistance of another person to obtain treatment for the event and has a plasma glucose level ≤ 70 mg/dL (≤ 3.9 mmol/L). The rescue treatment of hypoglycemia may include IV glucose or buccal or intramuscular glucagon.

The definition of severe symptomatic hypoglycemia includes all episodes in which neurological impairment was severe enough to prevent self-treatment and which were thus thought to place patients at risk for injury to themselves or others. Note that "requires assistance" means that the patient could not help himself or herself. Someone being kind that assists spontaneously the patient when not necessary does not qualify as "requires assistance."

Severe hypoglycemia will be qualified as a SAE only if it fulfills SAE criteria.

If a patient presents with symptoms of hypoglycemia, the Investigator will need to take immediate action to confirm the patient's glucose level and treat the patient accordingly.

The experience of hypoglycemia may vary greatly from patient to patient. However, there are certain classical signs and symptoms, of which patients should be aware as a clue that their blood glucose may be low. Common symptoms include headache, heart pounding, confusion, disorientation, numbness or tingling, pale skin, shakiness or tremulousness, increased appetite, anxiousness or nervousness, lightheadedness or dizziness, sweating, and weakness. Coma could occur if blood sugar correction is not performed.

If patients suspect they might be having a hypoglycemia reaction, they should check their blood glucose using their meters as soon as possible, before treatment if possible, provided they feel it is safe to do so. If there is doubt about safety they should treat the event first, using some sugar, milk, or juice for example, then obtain and record a blood glucose value as soon as possible thereafter. The time and nature of treatment should be noted, and especially if any blood glucose result was before or after treatment. It would be helpful for the patient to note if a contributory factor (e.g., missed or reduced meals, unaccustomed physical activity) occurred earlier in the day of the event.

8.5.8 Safety Monitoring for Hyperglycemia

Upward dose titration and/or addition of any other anti-hyperglycemic agent(s) will not be allowed during the course of the study, unless specific threshold values are met at Week 13 or later and confirmed on subsequent testing (ideally within 1-week of the initial test).

HbA1c is monitored every 3 months throughout the study. In addition, patients on insulin should self-monitor their plasma glucose (SMPG) routinely on a glucometer as per practice guidelines. If a fasting pre-breakfast SMPG value exceeds the specific glycemic limit, the patient should check it again on the following 2 days. If all the fasting pre-breakfast values on 3 consecutive days exceed the specific limit, the patient should contact the Investigator and an unscheduled central laboratory FPG measurement and HbA1c should be performed.

The threshold values are defined as:

- FPG > 270 mg/dL (15.0 mmol/L)
- HbA1c > 9% (for patients with baseline HbA1c < 8% and HbA1c increase of more than 1% from baseline (for patients with baseline HbA1c ≥ 8 and < 9%)

In case of confirmed FPG/HbA1c above the threshold value, the Investigator should ensure that no reasonable explanation exists for insufficient glucose control and in particular that:

- Plasma glucose was actually measured in the fasting condition (i.e., after at least 10 hours fast)
- Absence of intercurrent disease which may jeopardize glycemic control. In case of an emergency (e.g., surgery, infection), the Investigator can take appropriate measures for glycemic control
- Compliance to treatment is appropriate
- Compliance to diet and lifestyle is appropriate

If any of the above can reasonably explain the insufficient glycemic control, the Investigator should consider the following:

- Investigation and treatment of intercurrent disease (to be reported in adverse event (AE)/concomitant medication parts of the e-CRF)
- Stress on the absolute need to be compliant to treatment
- Organize a specific interview with a Registered Dietician or other qualified nutrition professional and stress on the absolute need to be compliant to diet and lifestyle recommendations

An FPG/HbA1c follow-up assessment should be arranged after appropriate action has been taken. If none from the above-mentioned reasons can be found, or if appropriate action fails to decrease FPG/HbA1c under the threshold values, additional medication may be introduced at the Investigator's discretion and according to local guidelines after discussion with the Sponsor Medical Monitor.

8.5.9 Acute Pancreatitis

If a patient has an episode of acute pancreatitis, treatment with Study Drug should be suspended temporarily until the patient is clinically stable. The suitability of the patient for continued treatment and the need for any modification to treatment schedule (refer to Section 8.7) will be determined by the Investigator in consultation with the Study Medical Monitor.

8.6 Stopping Rules

For the purposes of stopping rules, baseline is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1.

8.6.1 Stopping Rules for Liver Chemistry Elevations

In the event of laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor,** treatment of a patient with volanesorsen

will be stopped permanently; values that are not confirmed due to failure to retest or missing lab values will be presumed confirmed:

1. ALT or AST > 8 x ULN, which is confirmed
2. ALT or AST > 5 x ULN, which is confirmed and persists for ≥ 2 weeks
3. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed **and** total bilirubin > 2 x ULN or INR > 1.5
4. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed, and the new appearance (i.e., onset coincides with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> ULN) felt by the Investigator to be potentially related to hepatic inflammation

8.6.2 Stopping Rules for Renal Function Test Results

In the event of a persistent elevation that is observed over 2 consecutive weeks, for any of the 3 criteria below, treatment of a patient with volanesorsen may be stopped temporarily:

1. Serum creatinine increase that fulfill all of the following criteria: ≥ 0.3 mg/dL (26.5 µmol/L) and ≥ 40% above baseline creatinine values and > ULN
2. Proteinuria, dipstick 2 + (confirmed by dipstick retest and then further confirmed by a quantitative total urine protein measurement of > 1.0 g/24-hour)
3. Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault ≤ 40 mL/min that is confirmed by a 24-hour urine collection

The possible treatment re-initiation or follow-up schedule for any events meeting either of these criteria will be determined by the Investigator **in consultation with** the Sponsor Medical Monitor or designee.

8.6.3 Stopping Rules for Platelet Count Results

Actions to be taken in the event of a low platelet count are summarized in Table 3 below.

In the event of a platelet count less than 75,000/mm^3 that is associated with major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), treatment of a patient with volanesorsen will be stopped permanently. The follow-up schedule for any events meeting this stopping criterion will be determined by the Investigator in consultation with the Sponsor Medical Monitor.

In the event of any platelet count less than 50,000/mm^3, or a platelet count less than 75,000/mm^3 that occurs while the patient is treated at 300 mg every 2 weeks or 150 mg once-weekly then treatment of a patient with volanesorsen will be stopped permanently. Platelet count will be monitored as outlined in Table 3.

Administration of steroids is recommended for patients whose platelet count is less than 50,000/mm^3. Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or

Methylprednisolone 30 mg/kg/day for 7 days
(**note:** may require continuation with oral steroids after methylprednisolone). Triglyceride levels will be monitored weekly, and AE monitoring will continue, during cortiscosteroid treatment and the laboratory alert will be changed from an increase of 2,000 to 500 mg/dL during that period.

In the event of a platelet count less than 75,000/mm^3, and in the absence of major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), treatment of a patient with volanesorsen should be suspended temporarily until the platelet count has recovered to > 100,000/mm^3. If treatment is reinitiated it should be at a reduced dose frequency of 300 mg every 2 weeks or 150 mg once-weekly (refer to Section 8.7). The suitability of the patient for continued treatment will be determined by the Investigator in consultation with the Study Medical Monitor and will be based on factors such as the original rate of decline in the patient's platelet count, whether any bleeding events were experienced by the patient, and the speed of recovery of platelet count upon holding of treatment.

If after the first treatment re-challenge the platelet count again falls below 75,000/mm^3, then treatment of the patient with Study Drug will be stopped permanently.

Definition of Major Bleeding Events (Schulman et al. 2005):

- Fatal bleeding, and/or
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarterial or pericardial, or intramuscular with compartment syndrome, and/or
- Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more within 24 hours, or leading to transfusion of 2 or more units of whole or red cells

Definition of Clinically-Relevant, Non-Major Bleeding Events (Schulman et al. 2005):

1. Multiple-source bleeding
2. Spontaneous hematoma > 25 cm^2
3. Excessive wound hematoma (not injection site related)
4. Macroscopic hematuria (spontaneous or lasting > 24 hours if associated with an intervention)
5. Spontaneous rectal bleeding; epitasis, gingival bleeding, hemoptysis, hematemesis
6. Bleeding after venipuncture for > 5 minutes

Table 3 Actions in Patients with Low Platelet Count or Drop in Platelet Count

Platelet Count on Rx	Drug Dose	Monitoring
	Study Drug administration is contingent on the availability of the immediately preceding test result. An interpretable platelet value must be available within 7 days prior to treatment. Only the study doctor or qualified designee can authorize continued Study Drug administration based on an acceptable platelet value. Patients should not administer a dose until they have been contacted by their study doctor or designee and told that it is acceptable to dose. Authorization to dose must be documented in the patient's medical records.	**Monitor every 1 week unless otherwise specified** In addition, platelet function may be evaluated during the study by aggregometry, using an approved point-of-care diagnostic device, in some patients. This additional functional testing may be performed at selected study centers. Patients on dose pause should be monitored as per the platelet monitoring rules outlined in Section 8.8.1 until Study Drug administration is resumed. Obtain additional lab tests (Table 2) if 2 occurrences consecutive or non-consecutive) of platelet count 140K - > 100K/mm^3 or 1 occurrence of platelet count ≤ 100K/mm^3. Labs only need to be performed once. Labs may be collected over multiple visits, if blood requirements are a concern, as per Investigator discretion.
> 100K/mm^3	Once-weekly 300 mg Study Drug administration	
100K/mm^3 - >75K/mm^3	Permanently reduce dose frequency to 300 mg every 2 weeks or 150 mg once-weekly	
75K/mm^3 - >50K/mm^3	• If occurs while on dose of 300 mg every 2 weeks or 150 mg once-weekly then permanently discontinue Study Drug, otherwise dose pause. If dose pause is ≥ 3 months then patient must discontinue treatment and enter the follow up period. • When platelet count returns to > 100K/mm^3 restart treatment at dose frequency of 300 mg every 2 weeks or 150 mg once-weekly in consultation with the **Sponsor Medical Monitor**	• Monitor every 2-3 days until 2 successive values are > 75K/mm^3 then monitor every 1 week • Consider discontinuation of antiplatelet agents/NSAIDS/ anticoagulant medication

Platelet Count on Rx	Drug Dose	Monitoring
≤ 50K/mm^3	Permanently discontinue Study Drug and the patient will enter the follow up period	• Monitor daily until 2 successive values show improvement then monitor every 2-3 days until 2 successive values are > 75K/mm^3 then monitor every 1 week • Patient should be evaluated by a hematologist to provide diagnostic and therapeutic management • Steroids recommended*. It is strongly recommended that, unless the patient has a medical contraindication to receiving glucocorticoids, the patient receives glucocorticoid therapy to reverse the platelet decline. • Monitor triglyceride levels weekly and continue AE monitoring during steroid therapy • Discontinue antiplatelet agents/ NSAIDS/ anticoagulant medication while platelet count is < 50K/mm^3 if possible

* Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or methylprednisolone 30 mg/kg/day for 7 days (**note**: may require continuation with oral steroids after methylprednisolone)

8.7 Adjustment of Dose Frequency

Dose adjustments for platelet count reduction must be made in accordance with Section 8.6.3 and Table 3 (above).

Other dose adjustments, including dose interruptions, and/or decreasing the dose to 150 mg once-weekly or the dose frequency to 300 mg every 2 weeks will be allowed for safety and tolerability. Any proposed adjustment to treatment schedule must be discussed with, and approved by, the Study Medical Monitor prior to initiation. Up to 2 adjustments in the treatment schedule may be allowed.

Patients may be dose paused in response to AEs, and the Study Medical Monitor is informed. If a patient is dose paused for ≥ 3 months, he or she is considered to have discontinued treatment and should enter the 13-week post-treatment follow-up period.

8.8 Discontinuation of Study Treatment

A patient must permanently discontinue study treatment for any of the following:

- The patient becomes pregnant. Report the pregnancy according to instructions in Section 9.5.4.
- The patient withdraws consent.
- The patient experiences an AE that necessitates permanent discontinuation of study treatment.
- The patient develops laboratory test abnormalities that meet any of the stopping rules listed in Section 8.6.
- The patient is dose paused for ≥ 3 months.

The reason for discontinuation of study treatment must be recorded in the CRF and source documentation.

8.8.1 Follow-up Visits for Early Termination from Treatment Period

Any patient who discontinues early from the Treatment Period should be followed as per the platelet monitoring rules shown in in Section 8.6.3 for the first 6 weeks after discontinuing Study Drug. Following this period, if the platelet count is stable (at least 3 consecutive values that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3), the next platelet count should be taken within at least 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug. Any patient who discontinues treatment after Week 44 should also be strongly encouraged to attend a final follow-up visit (Week 65 visit assessments) approximately 13 weeks after their last dose of Study Drug.

A patient who discontinues early from treatment with stable platelet counts above the LLN at the time of treatment discontinuation will have platelet counts drawn every 2 weeks after discontinuing Study Drug for the first 6 weeks after the last dose of Study Drug. A subsequent platelet count should then be taken after an additional 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug.

If the patient declines or is unable to participate in the above, an early termination (ET) visit (Week 52 visit assessments) should be performed at the time of withdrawal, at a minimum, and ideally within 2 weeks from the last dose of Study Drug.

8.8.2 Follow-up Visits for Early Termination from Post-Treatment Follow-up Period

The patient who requests to withdraw from the study during the Post-Treatment Follow-up Period should be encouraged to follow the platelet monitoring rules shown in Table 3 in Section 8.6.3 for the first 6 weeks after discontinuing Study Drug. Following this period, if the platelet count is stable (at least 3 consecutive values that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3), the next platelet count should be taken within at least 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug. Patients should also be encouraged to undergo a final follow-up visit (Week 65 or Week 117 if terminating from the Extended Treatment Follow-Up Period), see Appendix A) prior to leaving the study.

If a patient withdraws due to an AE at any time during the study, the Investigator should arrange for the patient to have appropriate follow-up until the AE has resolved or stabilized.

8.9 Withdrawal of Patients from the Study

Patients must be withdrawn from the study for any of the following:

- Withdrawal of consent
- The patient is unwilling or unable to comply with the protocol

Other reasons for withdrawal of patients from the study might include:

- At the discretion of the Investigator for medical reasons
- At the discretion of the Investigator or Sponsor for noncompliance

- Significant protocol deviation

All efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information, including the reason for withdrawal from study, must be recorded in the CRF.

Any patient who withdraws consent to participate in the study will be removed from further treatment and study observation immediately upon the date of request. These patients should be encouraged to complete the ET study procedures and observations at the time of withdrawal (see Section 8.8 and Appendix A).

For patients withdrawn for reasons other than withdrawal of consent, every effort should be made to complete the early termination study procedures and observations at the time of withdrawal (see Section 8.8 and Appendix A).

8.10 Concomitant Therapy and Procedures

The use of concomitant therapies or procedures defined below must be recorded on the patient's CRF. AEs related to administration of these therapies or procedures must also be documented on the appropriate CRF.

8.10.1 Concomitant Therapy

A concomitant therapy is any non-protocol specified drug or substance (including over-the-counter medications, herbal medications and vitamin supplements) administered between signing informed consent and completion of the post-treatment follow-up period. All concomitant medications/treatments and significant non-drug therapies (including supplements and assistive devices) received by a patient, including changes in the patient's current medications, must be recorded in the patient's source documents and CRF. Patients taking over the counter (OTC) omega-3 fatty acids should make every effort to remain on the same brand throughout the study.

Allowed Concomitant Therapy

Any medications deemed necessary by the Investigator are allowed except those listed in the disallowed concomitant therapy.

Disallowed Concomitant Therapy

No lipid lowering therapies (e.g., fibrates, niacin, fish oil or other products containing omega-3 fatty acids [including over-the-counter preparations]), -glucagon-like peptide-1 (GLP-1) agonists, Glybera, or systemic corticosteroids may be started or adjusted after baseline qualification. Doses of existing oral anti-diabetic medication, oral contraceptives, hormone replacement therapy, anticoagulants, or drugs or dietary supplements with potential lipid-altering effects should not be adjusted. Study patients are prohibited from receiving other experimental agents during the study. This includes marketed agents at experimental dosages that are being tested for the treatment of hypertriglyceridemia.

Patients should consult with the Site Investigator or designee prior to initiating any new medication, including non-prescription or herbal compounds or any other non-drug therapy.

8.10.2 Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between signing of informed consent and Week 65 (or Week 117 if patient enters the extended treatment period) visit.

Disallowed Concomitant Procedure

Plasma apheresis is not allowed during the study.

8.11 Treatment Compliance

Compliance with treatment dosing is to be monitored and recorded by Study Center staff. The Study Center staff is required to document the receipt, dispensing, and return/destruction of volanesorsen. Patients that are self-administering volanesorsen at home must record treatment in a dosing diary that will be reviewed periodically by Study Center staff and the Clinical Monitor.

9. SERIOUS AND NON-SERIOUS ADVERSE EVENT REPORTING

9.1 Sponsor Review of Safety Information

Safety information will be collected, reviewed, and evaluated by the Sponsor in accordance with the Safety Management Plan throughout the conduct of the clinical trial.

9.2 Regulatory Requirements

The Sponsor is responsible for regulatory submissions and reporting to the Investigators of serious adverse events (SAEs) including suspected unexpected serious adverse reactions (SUSARs) per the International Conference on Harmonization (ICH) guidelines E2A and ICH E6 (R2). Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines.

Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) will be notified of any SAE according to applicable regulations. The Independent DSMB will be notified of any SAE as specified in the DSMB charter.

In addition to the Investigator's assessment of relatedness, the Sponsor or designee will evaluate the available information and perform an independent assessment of relatedness. While the Sponsor may upgrade an Investigator's decision it is not permissible to downgrade the Investigator's opinion for the purposes of determining whether the SAE meets the definition of a SUSAR.

The following table identifies the SAEs that the Sponsor or designee will not report on an individual basis in an expedited manner because they are anticipated to occur in the study population independent of volanesorsen exposure. The Investigator still has the responsibility to report all SAEs to the Sponsor as described in Sections 9.4.1 to 9.4.3.5.

Table 4 Expected Event for the Protocol Defined Population by Preferred Term and the Expected Incidence

Preferred Term	Expected Incidence in the Protocol Defined Population (Gaudet et al. 2010 and 2013)
Pancreatitis associated events including the PTs of hereditary pancreatitis, pancreatitis, pancreatitis acute, pancreatitis chronic, pancreatitis necrotizing, pancreatitis relapsing	0.2-0.35 events per patient-year

Fatal pancreatitis associated events will be considered as unexpected and are reportable. The Sponsor and DSMB will monitor non-fatal pancreatitis associated SAEs using the incidence rate of the event compared to the rate expected in a non-volanesorsen exposed population. If the aggregate analysis indicates that an event is occurring significantly more frequently or at a greater severity than expected, then the event will be reported.

SAEs not specified in the table will be evaluated on case by case basis to determine whether there is a reasonable possibility that the drug caused the event. If the event is considered by the Sponsor or designee to meet the definition of a SUSAR the event will be reported.

9.3 Definitions

9.3.1 Adverse Event

An adverse event is any unfavorable and unintended sign (including a clinically-significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the study or use of investigational drug product, whether or not the AE is considered related to the investigational drug product.

9.3.2 Adverse Reaction and Suspected Adverse Reaction

An adverse reaction is any adverse event caused by volanesorsen.

A suspected adverse reaction is any adverse event for which there is a reasonable possibility that volanesorsen drug caused the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

9.3.3 Serious Adverse Event (SAE)

A serious adverse event is any adverse event that in the view of either the Investigator or Sponsor, meets any of the following criteria:

- Results in death
- Is life threatening: that is, poses an immediate risk of death at the time of the event

An AE or suspected adverse reaction is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Hospitalization is defined as an admission of greater than 24 hours to a medical facility and does not always qualify as an AE
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly or birth defect in the offspring of the patient (whether the patient is male or female)
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

9.4 Monitoring and Recording Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the study (i.e., before informed consent) should be recorded as Medical History and not recorded as AEs unless the pre-existing condition worsened. The Investigator should always group signs and symptoms into a single term that constitutes a **single unifying diagnosis** if possible.

9.4.1 Serious Adverse Events

In the interest of patient safety, and in order to fulfill regulatory requirements, all SAEs (regardless of their relationship to volanesorsen) should be reported to the Sponsor or designee within 24 hours of the Study Center's first knowledge of the event. The collection of SAEs will begin after the patient signs the informed consent form and stop at the end of the patient's follow-up period which is defined as the Week 65 visit (or Week 117 if patient enters the extended treatment period). When the Investigator is reporting by telephone, it is important to speak to someone in person versus leaving a message. An Initial Serious Adverse Event Form should be completed and a copy should be faxed to the Sponsor or designee.

Detailed information should be actively sought and included on Follow-Up Serious Adverse Event Forms as soon as additional information becomes available. All SAEs will be followed until resolution. SAEs that remain ongoing past the patient's last protocol-specified follow-up visit will be evaluated by the Investigator and Sponsor. If the Investigator and Sponsor agree the patient's condition is unlikely to resolve, the Investigator and Sponsor will determine the follow-up requirement.

9.4.2 Non-Serious Adverse Events

The recording of non-serious AEs will begin after the patient signs the informed consent form and will stop at the end of the patient's follow-up period, which is defined as the Week 65 visit (or Week 117 if patient enters the extended treatment period). The Investigator will monitor each patient closely and record all observed or volunteered AEs on the Adverse Event Case Report Form.

9.4.3 Evaluation of Adverse Events (Serious and Non-Serious)

The Investigator's opinion of the following should be documented on the Adverse Event Case Report Form:

9.4.3.1 Relationship to the Study Drug

The event's relationship to volanesorsen is characterized by 1 of the following:

- **Related:** There is clear evidence that the event is related to the use of volanesorsen, e.g., confirmation by positive rechallenge test
- **Possible:** The event cannot be explained by the patient's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and volanesorsen administration
- **Unlikely/Remote:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to volanesorsen administration and/or exposure suggests that a causal relationship is unlikely (For reporting purposes, Unlikely/Remote will be grouped together with Not Related)
- **Not Related:** The event can be readily explained by the patient's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and volanesorsen

9.4.3.2 Severity

The severity of AEs and SAEs will be graded based on criteria from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010 (refer to Appendix D). Any AE not listed in Appendix D will be graded as follows:

- **Mild:** The event is easily tolerated by the patient and does not affect the patient's usual daily activities
- **Moderate:** The event causes the patient more discomfort and interrupts the patient's usual daily activities
- **Severe:** The event is incapacitating and causes considerable interference with the patient's usual daily activities

If the event is an SAE, then all applicable seriousness criteria must be indicated (criteria listed in Section 9.3.3).

9.4.3.3 Action Taken with Volanesorsen

Action taken with volanesorsen due to the event is characterized by 1 of the following:

- **None:** No changes were made to volanesorsen administration and dose
- **Permanently Discontinued:** Volanesorsen was discontinued and not restarted
- **Temporarily Interrupted, restarted – same dose:** Treatment was temporarily interrupted or delayed due to the AE and restarted at the same dose

- **Reduced schedule:** Treatment frequency was reduced

9.4.3.4 Treatment Given for Adverse Event

Any treatment (e.g., medications or procedures) given for the AE should be recorded on the Adverse Event Case Report Form (treatment should also be recorded on the concomitant treatment or ancillary procedures CRF as appropriate).

9.4.3.5 Outcome of the Adverse Event

If the event is a non-serious AE then the event's outcome is characterized by 1 of the following:

- **AE Persists:** Patient terminates from the trial and the AE continues
- **Recovered:** Patient recovered completely from the AE
- **Became Serious:** The event became serious (the date that the event became serious should be recorded as the Resolution Date of that AE and the Onset Date of the corresponding SAE)
- **Change in Severity** (if applicable): AE severity changed

If the event is a SAE then the event's outcome is characterized by 1 of the following:

- **Ongoing:** SAE continuing
- **Persists (as non-serious AE):** Patient has not fully recovered but the event no longer meets serious criteria and should be captured as an AE on the non-serious AE eCRF (the SAE resolution date should be entered as the date of onset of that AE)
- **Recovered:** Patient recovered completely from the SAE (the date of recovery should be entered as the SAE resolution date)
- **Fatal:** Patient died (the date of death should be entered as the SAE resolution date)

9.4.4 Adjudication Committees

All SAEs that occur during the study that are consistent with a major acute cardiovascular event (MACE) will be adjudicated by a blinded, independent committee as outlined in the MACE Adjudication Charter.

All AEs and SAEs that occur during the study that are consistent with an event of acute pancreatitis will be adjudicated by a blinded, independent committee according to the Atlanta classification of acute pancreatitis (Banks et al. 2013) and as outlined in the Pancreatitis Adjudication Charter. In addition, data for prior episodes of acute pancreatitis or suspected pancreatitis will be collected by review of each patient's medical chart and these events will also be adjudicated.

9.5 Procedures for Handling Special Situations

9.5.1 Abnormalities of Laboratory Tests

Clinically-significant abnormal laboratory test results may, in the opinion of the Investigator, constitute or be associated with an AE. Examples of these include abnormal laboratory results that are associated with symptoms, or require treatment, e.g., bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac arrhythmias due to hyperkalemia. Whenever possible, the underlying

diagnosis should be listed in preference to abnormal laboratory values as AEs. Clinically-significant abnormalities will be monitored by the Investigator until the parameter returns to its baseline value or until agreement is reached between the Investigator and Sponsor Medical Monitor. Laboratory abnormalities deemed not clinically-significant (NCS) by the Investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator should not be deemed NCS on the laboratory sheet.

The Investigator is responsible for reviewing and signing all laboratory reports. The signed clinical laboratory reports will serve as source documents and should include the Investigator's assessment of clinical significance of out of range/abnormal laboratory values.

9.5.2 Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the patient is hospitalized; the Study Center must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the patient's consent to participate in the study
- The condition that required the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the patient's consent to participate in the study and the timing of the procedure or treatment
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission

9.5.3 Treatment Errors

Volanesorsen treatment errors should be documented as Protocol Deviations. A brief description should be provided in the deviation, including whether the patient was symptomatic (list symptoms) or asymptomatic, and the event accidental or intentional.

Treatment details should be captured on the Treatment Case Report Form. If the patient takes a dose of volanesorsen that exceeds protocol specifications and the patient is symptomatic, then the symptom(s) should be documented as an AE and be reported per Section 9.4.

Should an overdose occur, the Investigator or designee should refer to the Guidance to Investigator's section of the Investigator's Brochure and contact the Sponsor or designee within 24 hours.

9.5.4 Contraception and Pregnancy

Male patients and female patients of childbearing potential must continue to use appropriate contraception with their partners, or refrain from sexual activity, as described in Section 6.3.1.

If a patient becomes pregnant or a pregnancy is suspected, or if a male patient makes or believes that he has made someone pregnant during the study, then the Study Center staff must be informed immediately. An Initial Pregnancy Form should be submitted to the Sponsor or designee **within 24**

hours of first learning of the occurrence of pregnancy. Follow-up information including delivery or termination is reported on Follow-up Pregnancy Forms and reported within 24 hours.

Payment for all aspects of obstetrical care, child or related care will be the patient's responsibility.

Female patients: If a suspected pregnancy occurs while on the study (including follow-up), a pregnancy test will be performed. The patient with a confirmed pregnancy will be immediately withdrawn from treatment with volanesorsen. However, the patient will be encouraged to complete the post-treatment follow-up portion of the study to the extent that study procedures do not interfere with the pregnancy. Regardless of continued study participation, the study physician will assist the patient in getting obstetrical care and the progress of the pregnancy will be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the Study Center and Sponsor may require access to the mother and infant's medical records for an additional 8 weeks after birth.

Male patients: The progress of the pregnancy in a male patient's partner should be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, **the Study Center and Sponsor may request access to the mother and infant's medical records for an additional 8 weeks after birth**. Follow-up will be performed to the extent permitted by applicable regulations and privacy considerations.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints

For fasting lipid measurements, the values at Month 3 analysis time point are defined as the average of Week 12 (Day 78) and Week 13 (Day 85) fasting assessments, the values of Month 6 analysis time point is at the end of Month 6 are defined as the average of Week 25 (Day 169) and Week 26 (Day 176) fasting assessments, and the values at the Month 12 analysis time point are defined as the average of Week 50 (Day 344) and Week 52 (Day 358) fasting assessments.

10.1.1 Efficacy Endpoints

- Percent change and absolute change from baseline in fasting TG
- Frequency and severity of patient reported abdominal pain during the treatment period
- Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-HDL-C, apoB, HDL-C, apolipoprotein A-1 (apoA-1), VLDL-C, and LDL-C
- Percent change from baseline in fasting total apolipoprotein C-III
- Change in blood viscosity (may be evaluated)
- Quality of Life questionnaires (EQ-5D, SF-36)
- Adjudicated acute pancreatitis event rate
- Other symptoms: eruptive xanthoma, lipemia retinalis

10.1.2 Safety Endpoints

- Adverse events including adjudicated events of pancreatitis and MACE
- Vital signs and weight
- Physical examinations
- Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis)
- Echocardiography
- Electrocardiograms (ECGs)
- Use of concomitant medications
- MRIs
- Platelet aggregation (may be evaluated)

10.2 Sample Size

No sample size calculations were performed as this is an open-label study.

10.3 Populations

Full Analysis Set (FAS): All patients who are enrolled and received at least 1 dose of active Study Drug and have a baseline TG assessment. The FAS represents the practically-feasible intent-to-treat (ITT) population as delineated in ICH Guideline E9.

Per Protocol Set (PPS): Subset of the FAS who received 9 of first 13 scheduled doses of volanesorsen and with no significant protocol deviations that would be expected to affect efficacy and PD assessments. The detailed criteria will be specified and finalized prior to the final database lock.

Safety Set: All patients who are enrolled and receive at least 1 dose of volanesorsen.

PK Population: All patients who are enrolled, receive at least 1 dose of volanesorsen, and have at least 1 post first dose PK sample collected, analyzed, and reported.

10.4 Definition of Baseline

Definitions of baseline are given below for the purposes of the final analysis.

For fasting lipid measurements, 2 baselines are defined for each patient in Groups 1 and 2: Group 1 (ISIS 304801-CS6) or Group 2 (ISIS 304801-CS16) index study baseline and the baseline in this open-label study, which is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 (e.g., qualification assessments or assessments from final visit of the ISIS 304801-CS6 or ISIS 304801-CS16 index studies if used for qualification). For Group 3 patients, the baseline for fasting lipid measurements is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 in this open-label study.

For other measurements, baseline for patients on active treatment in the ISIS 304801-CS6 or ISIS 304801-CS16 index study will be the ISIS 304801-CS6 or ISIS 304801-CS16 index study baseline. For patients on placebo in the ISIS 304801-CS6 or ISIS 304801-CS16 index study and Group 3 patients, baseline will be the last non-missing assessment prior to the first dose of Study Drug.

10.5 Interim Analysis

An interim analysis may be conducted after the last patient's Week 13 visit of the open-label study or after the database of the ISIS 304801-CS6 and ISIS 304801-CS16 index studies are locked and unblinded. Both safety and efficacy information from this open-label study may be summarized during this interim analysis. Efficacy analyses will be detailed in the SAP.

10.6 Planned Methods of Analysis

All eCRF data, lab data transfers, as well as any outcomes derived from the data, will be provided in the patient data listings. Patient data listings will be presented for all patients enrolled into the study. Descriptive summary statistics including n, mean, median, standard deviation, standard error, interquartile range (25th percentile, 75th percentile), and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data by treatment group of the index studies for patients on active in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies, and pooled treatment naive group which including patients on placebo in index studies and Group 3 patients. Where appropriate, p-values will be reported. All statistical tests will be conducted using 2-sided tests with 5% Type I error rates unless otherwise stated.

TG related endpoints will be assessed in the FAS and PPS, and all other efficacy endpoints will be assessed in the FAS. All safety assessments will be performed on the Safety Set. PK endpoints will be assessed in the PK Set as applicable.

10.6.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics by treatment group and overall. The patient disposition will be summarized by treatment group and overall. All patients enrolled will be included in a summary of patient disposition.

10.6.2 Safety Analysis

Treatment duration and amount of Study Drug received will be summarized by treatment group and overall.

Patient incidence rates of AEs will be tabulated by MedDRA system organ class, MedDRA preferred term, and treatment group of the index studies. Narratives of treatment-emergent deaths, serious and significant AEs, including early withdrawals due to AEs, will also be provided.

All treatment-emergent AEs, all treatment-emergent AEs potentially related to Study Drug, all treatment-emergent serious AEs, and all treatment-emergent serious AEs potentially related to Study Drug will be summarized.

Injection Site Reactions (ISRs) will be summarized by treatment group, MedDRA preferred term and severity.

Independently adjudicated events of MACE and pancreatitis will be summarized by treatment group.

Laboratory tests to ensure patient safety including chemistry panel, complete blood count (CBC) with differential, coagulation panel, IM, complement etc., will be summarized by study visits by treatment group.

These safety variables will also be presented as change and percent change from baseline over time after Study Drug administration, as appropriate.

Vital signs, weight, ECG measures, echocardiography assessments, and MRI assessments will be tabulated by treatment group.

10.6.3 Efficacy Analysis

Percent change and change from baseline to Month 3, Month 6, and Month 12 in fasting TG will be summarized by treatment group. Response rate of patients with fasting plasma TG < 750 mg/dL or achieving fasting TG ≥ 40% reduction from baseline at Month 3, Month 6, and Month 12 will be summarized. Response analysis will also be conducted using a range of fasting plasma TG thresholds for determination of responder status.

Percent change and change from baseline to Month 3, Month 6, and Month 12 will also be summarized by treatment group for other fasting lipid measures including non-HDL-C, apoB, HDL-C, apoA-1, VLDL-C, and LDL-C, total cholesterol, and fasting total apoC-III.

The incremental effects of volanesorsen on lipid measures will be explored and the association between changes in lipid parameters and total amount of drug received will be examined, as appropriate.

Frequency and severity of patient reported abdominal pain, adjudicated acute pancreatitis event rate, quality of life assessments, and comparison of other symptoms including eruptive xanthomas and lipemia retinalis will be summarized by treatment group.

Additional details of the analyses to be conducted will be provided in the SAP.

10.6.4 Pharmacokinetic and Immunogenicity Analysis

10.6.4.1 Pharmacokinetic Analysis

For all patients, pre-dose and post-treatment volanesorsen plasma concentrations will be summarized using descriptive statistics by treatment group and IM status.

For patients in the PK subgroup only, non-compartmental PK analysis of volanesorsen will be carried out on each individual patient data set using data collected in the open-label study from the intensive PK subgroup, following a single-dose (i.e., single-dose PK) or multiple doses (i.e., steady-state PK), depending on their earlier treatment in the index studies (Group 1 and 2 patients). On Week 1 Day 1 of the open-label study, patients who received placebo in the index study (and all patients in Group 3) will receive the first treatment of volanesorsen (single-dose PK), while patients who received volanesorsen in the index studies had been on volanesorsen treatment for 12 months (ISIS 304801-CS6) or 6 months (ISIS 304801-CS16), thus the PK data collected from these patients reflect steady-state PK. The maximum observed drug concentration (C_{max}) and the time taken to reach C_{max} (T_{max}) will be obtained directly from the concentration-time data. Area under the plasma concentration-time curve from time zero to 24 hours (AUC_{0-24h}) will be calculated using the linear trapezoidal rule. Apparent systemic (plasma) clearance after SC administration (CL_{0-24h} /F) will be calculated from CL_{0-24h}/F = Actual Dose/AUC_{0-24h}. Mean residence time (MRT) from time zero to 24 hours after the SC administration will be calculated from the equation, $MRT_{0-24h} = AUMC_{0-24h}/AUC_{0-24h}$, where $AUMC_{0-24h}$ is the area under the moment plasma concentration-

time curve from time zero to 24 hours after the SC administration. Other PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist.

Plasma PK parameters will be summarized using descriptive statistics by treatment group and IM status. Additional details regarding the PK analysis will be described in the SAP.

Population PK, PK/PD, and covariate analysis may be performed if deemed appropriate, and results will be reported separately.

10.6.4.2 Immunogenicity Analysis

Immunogenicity (IM) results (screen positive/negative, confirmed positive/negative or not evaluable, and when applicable, titer of anti-volanesorsen antibodies) before, during, and after treatment with Study Drug (volanesorsen) (i.e., sample [anti-drug antibody] ADA status) will be listed by their prior treatment in study ISIS 304801-CS6 or ISIS 304801-CS16 (Groups 1 and 2) and study day. Subject ADA status (positive/negative or not evaluable) for all evaluable patients, along with the study day associated with the first positive IM status emerged (T_{first}, i.e., onset of ADA development), the last positive IM status observed (T_{last}), the last ADA sample collection day, and subject - peak titer if applicable, will be listed by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16 (Groups 1 and 2) and study day. Subjects with positive anti-volanesorsen antibody status may be further classified (when applicable) as being either 'persistent', 'transient', or 'not determinable', if deemed appropriate.

Additionally, the sample and subject IM incidence (number) and incidence rate (percent) will be summarized as the total number and percent of evaluated subjects with antibody negative, positive, and unknown status by treatment group. Furthermore, onset and titer of the ADA response, if applicable, will be summarized as median, quartiles (25% and 75%), and range.

Additional details regarding the IM data analysis will be described in the SAP.

Potential relationships between immunogenicity results (e.g., IM status) and selected efficacy (e.g., % change in fasting TG from baseline at 3-, 6-, and 12-month endpoints), safety, and PK (e.g., C_{trough}) measures will be evaluated using graphical analysis and statistical analysis. These analyses will be either conducted and included in the study report, or data pooled and analyzed from all available Phase 2 and 3 studies and reported separately.

11. INVESTIGATOR'S REGULATORY OBLIGATIONS

11.1 Informed Consent

The written informed consent document should be prepared in the language(s) of the potential patient population, based on an English version provided by the Sponsor.

Before a patient's participation in the trial, the Investigator is responsible for obtaining written informed consent from the patient after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific qualification procedures or any Study Drug are administered. The patient must be given sufficient time to consider whether to participate in the study.

The acquisition of informed consent and the patient's agreement or refusal to notify his/her primary care physician should be documented in the patient's medical records and the informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion (not necessarily an Investigator). The original signed informed consent form should be retained in the Study Master File and in any other locations required by institutional policy, and a copy of the signed consent form should be provided to the patient.

11.2 Ethical Conduct of the Study

The Guidelines of the World Medical Association (WMA) Declaration of Helsinki dated October 2002 the applicable regulations and guidelines of current Good Clinical Practice (GCP) as well as the demands of national drug and data protection laws and other applicable regulatory requirements will be strictly followed.

11.3 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent form, other written patient information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by the Sponsor before recruitment of patients into the study and shipment of volanesorsen. A copy of the written approval of any other items/materials that must be approved by the Study Center or IEC/IRB must also be received by the Sponsor before recruitment of patients into the study and shipment of Study Drug. The Investigator's Brochure must be submitted to the IEC/IRB for acknowledgement.

The Investigator must submit to and, where necessary, obtain approval from the IEC/IRB, for all subsequent protocol amendments and changes to the informed consent document. The Investigator should notify the IEC/IRB of deviations from the protocol in accordance with ICH E6 (R2) Section 4.5.2. The Investigator should also notify the IEC/IRB of serious adverse events occurring at the Study Center and other adverse event reports received from the Sponsor, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study. Copies of the Investigator's reports, all IEC/IRB submissions and the IEC/IRB continuance of approval must be sent to the Sponsor.

11.4 Patient Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained. On the case report forms (CRF) or other documents submitted to the Sponsor, patients should be identified by unique initials and a patient study number only. Documents that are not for submission to the Sponsor (e.g., signed informed consent forms) should be kept in strict confidence by the Investigator.

In compliance with Federal and local regulations/ICH E6 (R2) Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the patient to permit named representatives to have access to his/her study-related records without violating the confidentiality of the patient.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments

Protocol amendments must be made only with the prior approval of the Sponsor. Agreement from the Investigator must be obtained for all protocol amendments and amendments to the informed consent document. The regulatory authority and IEC/IRB must be informed of all amendments and give approval for any amendments likely to affect the safety of the patients or the conduct of the trial. The Investigator **must** send a copy of the approval letter from the IEC/IRB to the Sponsor.

12.2 Study Termination

The Sponsor reserves the right to terminate the study according to the terms of the site contract. The Investigator reserves the right to terminate their participation in the study, according to the terms of the site contract. The Investigator/Sponsor should notify the IEC/IRB in writing of the trial's completion or early termination and send a copy of the notification to the Sponsor.

12.3 Study Documentation and Storage

An electronic case report form (eCRF) utilizing an Electronic Data Capture (EDC) application will be used for this study.

The Investigator should ensure that all appropriately qualified persons to whom he/she has delegated trial duties are recorded on a Sponsor-approved Delegation of Site Responsibilities Form.

Source documents are original documents, data, and records from which the patient's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, imaging, and correspondence. In this study, CRFs may not be used as source documents.

The Investigator and Study Center staffs are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation in accordance with Section 8 of ICH E6 (R2), suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Elements should include:

- Patient files containing completed CRFs, informed consents, and supporting copies of source documentation
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation and all correspondence to and from the IEC/IRB and the Sponsor
- If volanesorsen supplies are maintained at the Study Center, proof of receipt, volanesorsen Accountability Record, Return of volanesorsen for Destruction, final study volanesorsen reconciliation, and all volanesorsen-related correspondence

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

No study document should be destroyed without prior written agreement between the Sponsor or and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor.

12.4 Study Monitoring

The Sponsor representative and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the trial (e.g., CRFs and other pertinent data) provided that patient confidentiality is respected.

The Sponsor monitor is responsible for inspecting the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to patient medical records and other study-related records needed to verify the entries on the CRFs.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH E6 (R2) and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's Clinical Quality Assurance Department. Inspection of Study Center facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the trial conduct and compliance with the protocol, ICH E6 (R2), and applicable regulatory requirements.

To ensure the quality of clinical data a clinical data management review will be performed on patient data received by the Sponsor. During this review, patient data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or Study Center notifications will be sent to the Study Center for completion and return to Sponsor.

The Principal Investigator will sign and date the indicated places on the CRF. These signatures will indicate that the principal Investigator inspected or reviewed the data on the CRF, the data queries, and the Study Center notifications, and agrees with the content.

12.5 Language

Case report forms must be completed in English. Generic names for concomitant medications should be recorded in English if possible, unless it is a combination drug, then record the trade name in English.

All written information and other material to be used by patients and investigative staff must use vocabulary and language that are clearly understood.

12.6 Compensation for Injury

The Sponsor maintains appropriate insurance coverage for clinical trials and will follow applicable local compensation laws. Patients will be treated and/or compensated for any study-related illness/injury in

accordance with the information provided in the Compensation for Injury section of the Informed Consent document.

13. REFERENCES

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14. APPENDICES

Appendix A Schedule of Procedures

Appendix A Schedule of Procedures

Study Period		Screen/ Run In[a]	Qual[a]	Treatment Period																						Post Treatment Follow-up		
Study Week		-8 to -2	-2 to -1	Wk 1		Wk 4	Wk 6	Wk 8	Wk 10	Month 3		Wk 15 & 17	Wk 19	Wk 21 & 23	Month 6		Wk 28 & 30	Wk 32	Wk 34 & 36	Wk 38	Wk 40 & 42	Wk 44	Wk 46 & 48	Month 12		Wk 54 & 56	Wk 58	Wk 65
										Wk 12	Wk 13				Wk 25	Wk 26								Wk 50	Wk 52 or ET			
Study Day		-56 to -15	-14 to -7	1	2	22	36	50	64	78	85	99 & 113	127	141 & 155	169	176	190 & 204	218	232 & 246	260	274 & 288	302	316 & 330	344	358	372 & 386	400	449
Visit Window+/- Days		0	0	0	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	7	7
Informed Consent		X	X																									
Outpatient Visit		X	X	X	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X	X[l]	X[l]	X[l]	X[l]	X	X[l]	X[l]	X[l]	X	X[l]	X[l]	X[l]	X[l]	X	X[l]	X[l]	X
Inclusion/Exclusion Criteria		X	X																									
Medical History[b]		X																										
Vital Signs + body weight (+ height on Day 1 only)		X	X	X		X		X			X					X				X					X			X
Physical Examination		X		X							X					X				X					X			X
12- lead ECG (triplicate)		X									X					X				X					X			X
MRI (liver/spleen)		X																							X[m]			
Echocardiography		X														X[m]									X[m]			
Blood Draw (Fasting)[d]	Chemistry Panel	X	X	X		X		X			X		X			X		X		X		X			X		X	X
	CBC with Differential[c]	X	X	X ◄ Platelets are assessed each calendar week, visits do not have specified windows to allow flexibility of scheduling. ► X																									X
	Serum Lipid Panel	X	X	X		X		X		X	X				X	X				X				X	X			X
	Blood viscosity[e]			X							X					X									X			
	Platelet aggregation[e]		X	X							X					X									X			
	Coagulation (aPTT, PT, INR)	X	X					X			X					X				X					X			
	Hepatitis B, C, HIV	X																										
	hsCRP, HbA1c, FPG, and de-lipidated free glycerol	HbA1c		X							X					X									X			X
	Sedimentation Rate			X							X					X									X			X
	Complement (C5a, Bb)			X							X					X									X			X
	Troponin I	X		X							X					X									X			X
	Platelet Bound Autoantibodies[e]			X																								
	Plasma PK - Volanesorsen			X[n]	X	X		X			X					X				X					X			X
	Anti-Volanesorsen Antibodies			X		X		X			X					X				X					X			X

Study Period	Screen/ Run In[a]	Qual[a]	Treatment Period																							Post Treatment Follow-up		
Study Week	-8 to -2	-2 to -1	Wk 1		Wk 4	Wk 6	Wk 8	Wk 10	Month 3		Wk 15 & 17	Wk 19	Wk 21 & 23	Month 6		Wk 28 & 30	Wk 32	Wk 34 & 36	Wk 38	Wk 40 & 42	Wk 44	Wk 46 & 48	Month 12		Wk 54 & 56	Wk 58	Wk 65
									Wk 12	Wk 13				Wk 25	Wk 26								Wk 50	Wk 52 or ET			
Study Day	-56 to -15	-14 to -7	1	2	22	36	50	64	78	85	99 & 113	127	141 & 155	169	176	190 & 204	218	232 & 246	260	274 & 288	302	316 & 330	344	358	372 & 386	400	449
Visit Window+/- Days	0	0	0	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	7	7
FSH (women only, if applicable)	X																										
Serum Pregnancy Test[f]	X	X			X		X			X		X			X		X		X		X			X		X	X

Appendix A Schedule of Procedures *Continued*

Study Period		Screen/ Run In[a]	Qual[a]	Treatment Period																							Post Treatment Follow-up		
Study Week		-8 to -2	-2 to -1	Wk 1		Wk 4	Wk 6	Wk 8	Wk 10	Month 3		Wk 15 & 17	Wk 19	Wk 21 & 23	Month 6		Wk 28 & 30	Wk 32	Wk 34 & 36	Wk 38	Wk 40 & 42	Wk 44	Wk 46 & 48	Month 12		Wk 54 & 56	Wk 58	Wk 65
										Wk 12	Wk 13				Wk 25	Wk 26								Wk 50	Wk 52 or ET			
Study Day		-56 to -15	-14 to -7	1	2	22	36	50	64	78	85	99 & 113	127	141 & 155	169	176	190 & 204	218	232 & 246	260	274 & 288	302	316 & 330	344	358	372 & 386	400	449
Visit Window+/- Days		0	0	0	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	7	7
Blood Draw (Fasting)[d]	Archive blood sample for potential gene sequencing related to hypertriglyceridemia (Group 3; Group 2 if not available from index study)[i]	X																										
	Archived Serum & Plasma Samples[g]			X				X			X					X									X			X
Urinalysis[d]		X	X	X[o]		X		X			X[o]		X[o]			X[o]		X[o]		X[o]		X[o]			X[o]		X[o]	X[o]
Fundus Photography[h]		X																							X[m]			
Genetic testing for FCS diagnosis (if not available in medical history)[i]		X																										
Once-weekly Study Drug: SC Injection				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Symptom Diary (weekly)		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Period	Screen/ Run In[a]	Qual[a]	Treatment Period																							Post Treatment Follow-up		
Study Week	-8 to -2	-2 to -1	Wk 1		Wk 4	Wk 6	Wk 8	Wk 10	Month 3		Wk 15 & 17	Wk 19	Wk 21 & 23	Month 6		Wk 28 & 30	Wk 32	Wk 34 & 36	Wk 38	Wk 40 & 42	Wk 44	Wk 46 & 48	Month 12		Wk 54 & 56	Wk 58	Wk 65
									Wk 12	Wk 13				Wk 25	Wk 26								Wk 50	Wk 52 or ET			
Study Day	-56 to -15	-14 to -7	1	2	22	36	50	64	78	85	99 & 113	127	141 & 155	169	176	190 & 204	218	232 & 246	260	274 & 288	302	316 & 330	344	358	372 & 386	400	449
Visit Window+/- Days	0	0	0	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	7	7
Quality of Life Assessment(s)			X							X					X									X			X
Food/Drink Diary (quarterly)[j]			X							X					X									X			X
Diet/Alcohol Counseling[k]	X	X	X		X		X			X					X				X					X		X	X
Adverse Events	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a Screening and Qualification (Group 3) procedures performed (Please refer to Sections 3.4, 4.1, and 6.1.2)

b Patient charts will be reviewed in order to collect data for events of acute pancreatitis or suspected pancreatitis in the patient's medical history. Chart review may be conducted at any time during the study. These events will be adjudicated in the same manner as for events of pancreatitis during the study

c Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1 week and the result must be reviewed by the Investigator and confirmed to be acceptable before treatment can continue. All platelet count results will be promptly reviewed by the Investigator to determine if the count has met a stopping rule, or the dose reduction rule of 100,000/mm^3, or the dose pause rule of 75,000/mm^3. Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor

Appendix A Schedule of Procedures *Continued*

Legend Text *Continued*

d Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours. During treatment period urine and blood samples will be collected prior to Study Drug administration. Does not apply to 24-hour PK blood draw

e May be done. Blood viscosity and platelet aggregation in volanesorsen-treatment naïve patients only

f Females of childbearing potential only

g Serum and plasma samples will be collected and stored for follow-up exploration of laboratory findings and/or adverse events (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.) in this or subsequent clinical studies of volanesorsen

h If possible, fundus photography should be completed prior to administration of the first dose of Study Drug (Group 2 [ISIS 304801-CS16 roll-over patients] and Group 3) and repeated at Week 52 (Please refer to Section 6.2.2.2)

i Genetic testing can be conducted for study qualification (Group 2 [ISIS 304801-CS16 roll-over patients] and Group 3); genetic testing will only be conducted if allowed in the geographic region and only after the patient has given specific written informed consent for genetic testing. A blood sample for potential gene sequencing may be collected at timepoints other than Screening or Qualification Visits.

j In addition to diary, patients will be contacted at random times during the study to review their current eating and drinking habits

k To reinforce compliance to the diet and alcohol restrictions. Random diet/alcohol assessments (phone visits) will also be performed by dietician or study personnel

l Assessments and procedures to be conducted by either a home healthcare nurse, or the Study Center as arranged by the Study Center personnel

m A ± 7-day window is allowed for MRI, echocardiography procedures and fundus photography

n Full or abbreviated PK profile (see Appendix C)

o Expanded urinalysis (see Appendix B)

Appendix A Schedule of Procedures – Extended Treatment Period

Study Period		Treatment Period																Post-Treatment Follow-up		
Study Week		**Wk 54 & 56**	**Wk 58**	**Wk 60 & 62**	**Mo 15 Wk 64**	**Wk 66 & 68**	**Wk 70**	**Wk 72 & 74**	**Mo 18 Wk 76**	**Wk 78 & 80**	**Wk 82**	**Wk 84, 86, & 88**	**Mo 21 Wk 90**	**Wk 92 & 94**	**Wk 96**	**Wk 98, 100 & 102**	**Mo 24 Wk 104**	**Wk 106 & 108**	**Wk 110**	**Mo 27 Wk 117**
Study Day		**372 & 386**	**400**	**414 & 428**	**442**	**456 & 470**	**484**	**498 & 512**	**526**	**540 & 554**	**568**	**582, 596 & 610**	**624**	**638 & 652**	**666**	**680, 694 & 708**	**722**	**736 & 750**	**764**	**813**
Visit Window+/- Days		**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**7**	**7**
Outpatient Visit		X[f]	X[f]	X[f]	X	X[f]	X[f]	X[f]	X	X[f]	X[f]	X[f]	X	X[f]	X[f]	X[f]	X	X[f]	X[f]	X
Vital Signs (+ body weight)					X				X				X				X			X
Physical Examination									X								X			
12- lead ECG (triplicate)									X								X			
Urinalysis(including P/C ratio)			X		X		X		X		X		X		X		X		X	X
Blood Draw (Fasting)[b]	Chemistry Panel		X		X		X		X		X		X		X		X		X	X
	CBC with Differential[a]	X Platelets are assessed each calendar week, visits do not have specified windows to allow flexibility of scheduling.																		X
	Serum Lipid Panel				X				X				X				X			X
	Coagulation (aPTT, PT, INR)				X				X				X				X			
	Troponin I				X				X				X				X			X
	Plasma PK - ISIS 304801[c]								X								X			X
	Anti-ISIS 304801 Antibodies								X								X			X
	Serum Pregnancy Test[d]		X		X		X		X		X		X		X		X		X	X
	Platelet Function [g]	X May be assessed at various timepoints, visits do not have specified windows to allow flexibility of scheduling.																		
Once-weekly Study Drug: SC Injection		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Diet/Alcohol Counseling[e]					X				X				X				X			
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Period	**Treatment Period**																**Post-Treatment Follow-up**		
Study Week	**Wk 54 & 56**	**Wk 58**	**Wk 60 & 62**	**Mo 15 Wk 64**	**Wk 66 & 68**	**Wk 70**	**Wk 72 & 74**	**Mo 18 Wk 76**	**Wk 78 & 80**	**Wk 82**	**Wk 84, 86, & 88**	**Mo 21 Wk 90**	**Wk 92 & 94**	**Wk 96**	**Wk 98, 100 & 102**	**Mo 24 Wk 104**	**Wk 106 & 108**	**Wk 110**	**Mo 27 Wk 117**
Study Day	**372 & 386**	**400**	**414 & 428**	**442**	**456 & 470**	**484**	**498 & 512**	**526**	**540 & 554**	**56 8**	**582, 596 & 610**	**624**	**638 & 652**	**666**	**680, 694 & 708**	**722**	**736 & 750**	**764**	**813**
Visit Window+/- Days	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**7**	**7**
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Appendix A Schedule of Procedures – Extended Treatment Period *Continued*

Legend Text

a Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1 week and the result must be reviewed by the Investigator and confirmed to be acceptable before treatment can continue. All platelet count results will be promptly reviewed by the Investigator to determine if the count has met a stopping rule, or the dose reduction rule of 100,000/mm^3, or the dose pause rule of 75,000/mm^3. Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor.

b Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours. During treatment period urine and blood samples will be collected prior to Study Drug administration

c Abbreviated PK collection (see Appendix C)

d Females of childbearing potential only

e To reinforce compliance to the diet and alcohol restrictions

f Assessments and procedures to be conducted by either a home healthcare nurse, or the Study Center as arranged by the Study Center personnel

g May be done

Appendix B List of Laboratory Analytes

Appendix B List of Laboratory Analytes

Based on emerging data from this or future studies, additional tests not listed below may be performed on stored samples to better characterize the profile of volanesorsen or other similar oligonucleotides.

Clinical Chemistry Panel

- Sodium
- Potassium
- Chloride
- Bicarbonate
- Total protein
- Albumin
- Calcium
- Magnesium
- Phosphorus
- Glucose
- BUN
- Creatinine
- Uric Acid
- Total bilirubin
- Direct (conjugated) bilirubin
- Indirect (unconjugated) bilirubin
- ALT
- AST
- Alkaline phosphatase

Screening Tests (Group 3)

- Hepatitis B surface antigen
- Hepatitis C antibody
- HIV antibody
- FSH (women only)
- Serum βhCG (women only)

Coagulation

- aPTT (sec)
- PT (sec)
- INR

Lipid Panel

- Total Cholesterol
- LDL-C
- HDL-C
- Triglycerides
- Non-HDL-C
- VLDL-C
- apoA-1
- apoB
- apoC-III

Hematology

- Red blood cells
- Hemoglobin
- Hematocrit
- MCV, MCH, MCHC
- Platelets
- White blood cells
- WBC Differential (% and absolute)
  - Neutrophils
  - Eosinophils
  - Basophils
  - Lymphocytes
  - Monocytes

Pharmacokinetics[1] & Immunogenicity

- Volanesorsen levels in plasma
- Anti-volanesorsen antibodies in plasma

Other Assessments

- hsCRP
- Sedimentation Rate
- C5a, Bb
- Troponin I[2]
- CK-MB[2]
- Platelet Bound Autoantibodies[3]
- De-lipidated free glycerol
- HbA1c, FPG
- Blood viscosity[3]

Urinalysis

- Color
- Appearance
- Specific gravity
- pH
- Protein
- Blood
- Ketones
- Urobilinogen
- Glucose
- Bilirubin
- Leukocyte esterase
- Nitrate
- Microscopic examination[4]

Additional Measures for Expanded Urinalysis

- Total protein (quantitative)
- Microalbumin
- β2-microglobulin

Platelet Function

- Platelet aggregation[3]
- Platelet Function[5]

1 Plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, IM testing (or possibly for purposes of IM assay development and/or validation), or to assess other actions of volanesorsen with plasma constituents

2 All abnormal troponin samples will be rerun at the central laboratory and also analyzed for CK-MB

3 May be done

4 Will be performed on abnormal findings unless otherwise specified

5 May be done using a point-of-care device on site

Appendix C Pharmacokinetic Sampling Schedule

Appendix C Pharmacokinetic Sampling Schedule

Blood samples for the determination of plasma volanesorsen concentrations will be collected prior to treatment, and at various times throughout the treatment and post-treatment follow-up period as noted in the tables below.

PK Sampling Schedule (All Patients except PK Subgroup)

Week	Wk 1	Wk 4	Wk 8	Wk 13	Wk 26	Wk 38	Wk 52	Wk 65#
Study Day	**D1**	**D22**	**D50**	**D85**	**D176**	**D260**	**D358**	**D449**
Visit Window +/- Days	0	2	2	2	2	3	2	7
Time Point	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime

Week 65 PK collection will be omitted for patients continuing to receive volanesorsen beyond Week 52

PK Sampling Schedule (PK Subgroup only*)

Week	Wk 1	Wk 1	Wk 4	Wk 8	Wk 13	Wk 26	Wk 38	Wk 52	Wk 65#
Study Day	**D1**	**D2**	**D22**	**D50**	**D85**	**D176**	**D260**	**D358**	**D449**
Visit Window +/- Days	0	0	2	2	2	2	3	2	7
Time Point	Pre-dose, 1, 2, 3, 4, 6, 8, and 12 hrs post-dose	24 hrs post-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime

* Patients at selected sites will be asked to participate in the extended 24-hour PK profile beginning on Study Day 1. Participation is optional

Week 65 PK collection will be omitted for patients continuing to receive volanesorsen beyond Week 52

PK Sampling Schedule (Extended Treatment Period)

Week	Wk 76	Wk 104	Wk 117
Study Day	**D526**	**D722**	**D813**
Visit Window +/- Days	2	2	7
Time Point	Pre-dose,	Pre-dose	Anytime

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

The following grading recommendations for adverse events relating to lab test abnormalities are based upon the **Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010**

Adverse Event	Mild	Moderate	Severe
Hematology			
aPTT prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage
Eosinophils increased†	650 – 1,500 cell/mm^3	1,501 - 5,000 cell/mm^3	>5,000 cell/mm^3
Fibrinogen decreased	<1.0 - 0.75 x LLN or <25% decrease from baseline	<0.75 - 0.5 x LLN or 25 - <50% decrease from baseline	<0.5 x LLN or ≥50% decrease from baseline
Hemoglobin decreased (Anemia)	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated
Hemoglobin increased	Increase in >0 - 2 g/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 g/dL above ULN or above baseline if baseline is above ULN	Increase in >4 g/dL above ULN or above baseline if baseline is above ULN
INR increased	>1 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation
Lymphocyte count decreased	<LLN - 800/mm^3; <LLN - 0.8 x 10^9/L	<800 - 500/mm^3; <0.8 - 0.5 x 10^9 /L	<500 /mm^3; <0.5 x 10^9 /L
Lymphocyte count increased	-	>4000/mm^3 - 20,000/mm^3	>20,000/mm^3
Neutrophil count decreased	<LLN - 1500/mm^3; <LLN - 1.5 x 10^9 /L	<1500 - 1000/mm^3; <1.5 - 1.0 x 10^9 /L	<1000/mm^3; <1.0 x 10^9 /L
Platelet count decreased	<LLN - 75,000/mm^3; <LLN - 75.0 x 10^9 /L	<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9 /L	<50,000/mm^3; <50.0 x 10^9 /L
White blood cell decreased	<LLN - 3000/mm^3; <LLN - 3.0 x 10^9 /L	<3000 - 2000/mm^3; <3.0 - 2.0 x 10^9 /L	<2000/mm^3; <2.0 x 10^9 /L
Chemistry			
Acidosis	pH <normal, but **>=**7.3	-	pH <7.3
Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Alkalosis	pH >normal, but ≤7.5	-	pH >7.5
Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 x ULN
Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

Adverse Event	Mild	Moderate	Severe
Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer
CD4 lymphocytes decreased	<LLN - 500/mm^3; <LLN - 0.5 x 10^9 /L	<500 - 200/mm^3; <0.5 - 0.2 x 10^9 /L	<200/mm^3; <0.2 x 10^9 /L
CPK increased*	>ULN - <6 ULN	6 - 10 x ULN	>10 x ULN
Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 x ULN
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 mg/dL; >3.1 mmol/L; Ionized calcium >1.6 mmol/L; hospitalization indicated
Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 mg/dL; >13.9 mmol/L; hospitalization indicated
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0; hospitalization indicated
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 mg/dL; >1.23 mmol/L
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 mmol/L; hospitalization indicated
Hyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 mg/dL; <1.75 mmol/L; Ionized calcium <0.9 mmol/L; hospitalization indicated
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 mg/dL; <3.0 mmol/L	<40 mg/dL (<2.2 mmol/L) AND requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions‡
Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 mmol/L; hospitalization indicated
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 mg/dL; <0.4 mmol/L
Hyponatremia	<LLN - 130 mmol/L	-	<130 mmol/L
Hypophosphatemia	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 mg/dL; <0.6 mmol/L
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

Adverse Event	Mild	Moderate	Severe
Urine			
Proteinuria Adults Children	1+ proteinuria; urinary protein <1.0 g/24 hrs -	2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs; Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Urinary protein ≥3.5 g/24 hrs; Urine P/C >1.9
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated

[†]Grading for this parameter is derived from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007

*Grading for this parameter is derived from the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0, Nov 2014

[‡]Modified for consistency with the ADA and Endocrine Society Guidelines (Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. Diabetes Care 2013;36:1384-95)

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ISIS 304801-CS7

The APPROACH Open-Label Study

Volanesorsen (ISIS 304801)

An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol Amendment 8 - France – 10 April 2017

EudraCT No: 2015-003755-21

ISIS 304801-CS7

The APPROACH Open-Label Study

Volanesorsen (ISIS 304801)

An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol Amendment 8 - France – 10 April 2017

Protocol History:

Original Protocol:	28 August 2015
Protocol Amendment 1:	2 February 2016
Protocol Amendment 2:	22 April 2016
Protocol Amendment 3:	9 May 2016
Protocol Amendment 4:	6 June 2016
Protocol Amendment 5:	19 August 2016
Protocol Amendment 6:	16 September 2016
Protocol Amendment 7:	3 February 2017

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MD, MBA
[redacted]

Ionis Protocol Number: ISIS 304801-CS7

Protocol Amendment 8 - France

EudraCT No: 2015-003755-21

Clinical Phase: 3

The APPROACH Open-Label Study

Volanesorsen (ISIS 304801)

An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

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Date: 10 April 2017

Confidentiality Statement

This document contains confidential information of Ionis Pharmaceuticals, Inc., that must not be disclosed to anyone other than the recipient study staff and members of the independent ethics committee, institutional review board, or authorized regulatory agencies. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc.

Protocol Signature Page

Protocol Number:	ISIS 304801-CS7
Protocol Title:	An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Amendment:	Amendment 8 - France
Date:	10 April 2017

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)", dated 10 April 2017, and agree to conduct the study as described herein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice (E6).

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc.

Investigator's Signature

Investigator's Name *(please print)*

Date (DD Month YYYY)

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PROTOCOL AMENDMENT

Protocol Number:	ISIS 304801-CS7
Protocol Title:	An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Amendment Number:	8 - France
Amendment Date:	10 April 2017

The purpose of this protocol amendment is to implement the following modifications to Protocol ISIS 304801-CS7 Amendment 7 dated 3 February 2017:

1. To update the platelet safety monitoring rules shown in Table 3.
2. To assess acute pancreatitis in medical history in Group 2 patients.
3. Added archive blood sample for potential gene sequencing related to hypertriglyceridemia (Group 2 if not available from index study).
4 Added Troponin I and platelet bound autoantibody testing at baseline (may be done) to provide added patient safety; blood viscosity (may be done) to assess potential benefit of ISIS 304801 administration; and platelet aggregation (may be done) to assess platelet function.

Minor changes (not included in the list of changes below) have been made throughout the protocol to correct errors and/or to improve the overall clarity of the original protocol but these changes do not impact subject safety, exposure, or the overall study design.

The following table provides a summary list of major changes to the protocol, additions are indicated as underline and deletions are indicated as strikethrough:

Protocol Section	Description of Change	Rationale
Section 3.4.3 Post-Treatment	The post-treatment evaluation period is at least 26 weeks and consists of at least ~~6~~9 Study Center visits on Weeks 53, 54, 55, 56, 57, 58, 65, 71, and 78 (Weeks 53, 54, 55, 56, 57, 58, and 71 may be conducted by a home healthcare nurse).	To provide added patient safety regarding platelet count reductions and ISIS 304801 dose exposure

Protocol Section	Description of Change	Rationale
Synopsis Section 5.1 Inclusion Criteria	3. Groups 1 and 2: Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement. Group 2: Patients who enrolled in ISIS 304801-CS16 must also meet the following criteria in order to enter into the open-label study: a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L) b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) supported by documentation of at least 1 of the following: • Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1) • Post heparin plasma LPL activity of ≤ 20% of normal in medical history. Note: testing of LPL activity should not be performed to confirm eligibility for the study c. Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 index study 4. Able and willing to participate in a 78-week study	To clarify that either genetics or LPL activity can be used as an inclusion criteria and that LPL activity should not be performed unless already in medical history
6.1.2 Treatment Period	During the treatment period, patients will report to the study center for clinic visits a minimum of 5 times during Weeks 1-52 (see Schedule of Procedures in Appendix A). Study Drug will be administered once weekly unless the patient is on a biweekly dosing schedule for safety reasons (Section 8.1). Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), AEs, concomitant medication/procedure information, lipid panel, blood viscosity, volanesorsen plasma concentrations, immunogenicity (IM) testing, platelet aggregation, liver/spleen MRI, ECGs, echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Adverse events at the injection site should be collected as adverse events. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period and all patients will complete a daily food diary for one week prior to their quarterly visit. All blood and urine samples should be collected prior to volanesorsen administration. Blood sampling at Weeks 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 39, 40, 41, 42, ~~43~~, 44, 45, 46, 47, 48, 49, 50, and 51 may be conducted by a home healthcare nurse. Approval for study procedures to be conducted by a home healthcare nurse on other outpatient visit days will require prior approval by the Sponsor. Patients must be fasted prior to drawing all blood samples and samples drawn locally should also be sent to the central laboratory for analysis whenever possible. ~~Every effort should be made to ensure the previous week's dose is given 7 days prior to a scheduled clinic visit.~~ Dosing instructions and training will be provided to the patient where applicable.	To provide added patient safety regarding platelet count reductions and ISIS 304801 dose exposure
6.1.4 Post-Treatment Period	After completion of the Week 52 visit assessments, patients will enter the at least 26-week post-treatment evaluation period or will participate in an expanded access program pending approval by the IRBs/IEC, and the appropriate regulatory authorities. The 26-week period consists of at least ~~6~~9 Study Center visits on Weeks 53, 54,55, 56, 57, 58, 65, 71, and 78 (Weeks 53, 54, 55, 56, 57, 58, and 71 may be conducted by a home healthcare nurse), as outlined in the Schedule of Procedures in Appendix A.	To provide added patient safety regarding platelet count reductions and ISIS 304801 dose exposure

Protocol Section	Description of Change	Rationale
6.2.1 Laboratory Assessments	Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1-week and the result must be reviewed by the Investigator and confirmed to be acceptable before dosing can continue. All platelet count results will be promptly reviewed by the Investigator to determine if the count has met a stopping rule, or the dose reduction rule of 100,000/mm^3, ~~and determined not to have met a stopping rule before dosing can continue~~ or the dose pause rule of 75,000/mm^3. ~~If there is no reportable platelet count within 14 days of the last platelet count, the Investigator will contact the patient to hold dosing until a new platelet count is obtained and reviewed.~~ ~~All platelet count results will be promptly reviewed by the Investigator to ensure that the count has not met the stopping rule and to determine whether the rate of decline is suggestive that the patient could be approaching the dose pause rule of 75,000/mm^3.~~ Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor.	To provide added patient safety regarding platelet count reductions, ISIS 304801 dose exposure, and treatment recommendations
6.2.10 Chart Review for Incidents of Acute Pancreatitis in Medical History (Group 2)	**Added** 6.2.10 Chart Review for Incidents of Acute Pancreatitis in Medical History (Group 2) Patient records will be reviewed for incidents of acute pancreatitis occurring up to 5 years prior to screening and information relating to these events will be collected for independent adjudication.	To assess acute pancreatitis in medical history in Group 2 patients
8.1 Volanesorsen Administration	**Removed** ~~Every effort should be made to ensure the previous week's dose is given 7 days prior to a scheduled clinic visit.~~	Dosing recommendations provided in updated monitoring and drug administration updates
8.5.2 Safety Monitoring for Platelet Count Results	Actions to be taken in the event of reduced platelet count are shown in Table ~~2~~3 in Section 8.6.3. Monitor every 1 week unless otherwise specified. Study Drug administration is contingent on the availability of the immediately preceding test result. An interpretable platelet value must be available within 7 days prior to dosing. Only the study doctor or qualified designee can authorize continued Study Drug administration based on an acceptable platelet value. Patients should not administer a dose until they have been contacted by their study doctor or designee and told that it is acceptable to dose. Authorization to dose must be documented in the patient's medical records. Due to the 1 to 2-year study duration it is anticipated that patients may undertake travel including vacations, which may impede weekly platelet monitoring. In some situations, it may be possible to arrange for local laboratory testing or use of the home healthcare service at their temporary location. The intent is to maintain weekly platelet monitoring and dosing where possible, as well as Investigator site contact with the study patients. However, if the above options are not possible, a temporary interruption of study treatment will be planned with a prompt blood draw upon the patient's return which must be reported and reviewed by the Investigator prior to the patient resuming dosing.	To provide added patient safety regarding platelet count reductions, ISIS 304801 dose exposure, and treatment recommendations

<table>
<tr><th>Protocol Section</th><th>Description of Change</th><th>Rationale</th></tr>
<tr><td>8.5.2 Safety Monitoring for Platelet Count Results
Continued</td><td>
The tests outlined in Table 2 should also be performed as soon as possible. Additional lab tests will be determined by the Sponsor Medical Monitor or designee in consultation with the Investigator.
Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor (See also Stopping Rules Section 8.6.3).
Table 2 Labs to Be Performed in the Event of a Platelet Count Less than the Lower Limit of Normal (x2) or < 100,000/mm^3 (x1)*
*In patients who have any 2 occurrences (consecutive or non-consecutive) of platelet count less than the lower limit of normal or who have any 1 occurrence of platelets < 100,000/mm^3. Labs only need to be performed once. Labs may be collected over multiple visits, if blood requirements are a concern, as per Investigator discretion.
Note: The following labs may change as additional data is assessed, and sites will be updated regarding any changes.

Added Table 2:
<table>
<tr><th>To Be Performed at Local Lab</th></tr>
<tr><td>Peripheral smear (should be performed locally, fixed and sent to central lab for review)</td></tr>
<tr><td>Fibrinogen split products or D-dimer on fresh blood</td></tr>
<tr><th>To Be Performed at Central Lab</th></tr>
<tr><td>Citrated sample for platelets</td></tr>
<tr><td>Coagulation panel (PT/INR, aPTT)</td></tr>
<tr><td>CBC with reticulocytes</td></tr>
<tr><td>Folate (folic acid)</td></tr>
<tr><td>Vitamin B12</td></tr>
<tr><td>Fibrinogen</td></tr>
<tr><td>von Willebrand factor</td></tr>
<tr><td>Total globulins, total IgA, IgG and IgM</td></tr>
<tr><td>Complement: total C3, total C4, Bb, C5a</td></tr>
<tr><td>hsCRP</td></tr>
<tr><td>Helicobacter pylori (breath test)</td></tr>
<tr><td>Serology for:</td></tr>
<tr><td>HBV, HCV, HIV (if not done recently for screening)</td></tr>
<tr><td>Rubella</td></tr>
<tr><td>CMV</td></tr>
<tr><td>EBV</td></tr>
<tr><td>Parvo B19</td></tr>
<tr><td>Auto-antibody screen:</td></tr>
<tr><td>Antiphospholipid</td></tr>
<tr><td>Rheumatoid factor</td></tr>
<tr><td>Anti-dsDNA</td></tr>
<tr><td>Anti-thyroid</td></tr>
<tr><th>To Be Performed at Specialty Lab(s)</th></tr>
<tr><td>Antiplatelet antibodies and Anti-PF4 assay</td></tr>
<tr><td>Anti-ASO antibody</td></tr>
</table>
</td><td>To provide added patient safety regarding platelet count reductions, ISIS 304801 dose exposure, and treatment recommendations</td></tr>
</table>

Protocol Section	Description of Change	Rationale
Section 8.6.3 Stopping Rules for Platelet Count Results	Actions to be taken in the event of a low platelet count are summarized in Table ~~2~~3 below. In the event of a platelet count less than 75,000/mm^3 that is associated with major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with volanesorsen will be stopped permanently. The follow-up schedule for any events meeting this stopping criterion will be determined by the Investigator in consultation with the Sponsor Medical Monitor. In the event of any platelet count less than 50,000/mm^3, or a rate of decline ≥ 50% between two consecutive assessments, irrespective of the platelet level, or a platelet count less than 75,000/mm^3 that occurs while the patient is on dosing at 300 mg every 2 weeks ~~or 150 mg every week~~ then dosing of a patient with volanesorsen will be stopped permanently. Platelet count will be monitored as outlined in Table 3. ~~daily until 2 successive values show improvement then monitored every 2-3 days until platelet count is stable.~~ Administration of steroids is recommended for patients whose platelet count is less than ~~25~~50,000/mm^3. Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (note: may require continuation with oral steroids after methylprednisolone). In order to reduce the unlikely but potential increased risk of pancreatitis during the period of corticosteroid therapy, triglyceride levels will be monitored weekly, and AE monitoring will continue, during corticosteroid treatment and the laboratory alert will be changed from an increase of 2,000 to 500 mg/dL during that period. In the event of a platelet count less than 75,000/mm^3, and in the absence of major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with volanesorsen should be suspended temporarily until the platelet count has recovered to > 100,000/mm^3. If dosing is continued it should be at a reduced dose frequency of 300 mg every 2 weeks ~~or a reduced dose of 150 mg per week~~ (refer to Section 8.7). The suitability of the patient for continued dosing will be determined by the Investigator in consultation with the Study Medical Monitor and will be based on factors such as the original rate of decline in the patient's platelet count, whether any bleeding events were experienced by the patient, and the speed of recovery of platelet count upon holding of dosing. If after the first dosing rechallenge the platelet count again falls below 75,000/mm^3, then dosing of the patient with Study Drug will be stopped permanently. ~~Following a rechallenge platelet count should be tested every week until count is stable.~~ ~~Any unreportable platelet count result must be rechecked and determined not to have met a stopping rule before dosing can continue.~~ ~~If there is no reportable platelet count within 14 days of the last platelet count, the Investigator will contact the patient to hold dosing until a new platelet count is obtained and reviewed.~~	To provide added patient safety regarding platelet count reductions, ISIS 304801 dose exposure, and treatment recommendations

<table>
<tr><th>Protocol Section</th><th>Description of Change</th><th>Rationale</th></tr>
<tr><td>Section 8.6.3 Stopping Rules for Platelet Count Results
Continued</td><td>
Table ~~2~~3 Actions in Patients with Low Platelet Count
<table>
<tr><th>Platelet Count on Rx</th><th>Drug Dose</th><th>Monitoring</th></tr>
<tr><td>~~Normal range, > 140K/mm^3~~</td><td>Study Drug administration is contingent on the availability of the immediately preceding test result. An interpretable platelet value must be available within 7 days prior to dosing. Only the study doctor or qualified designee can authorize continued Study Drug administration based on an acceptable platelet value. Patients should not administer a dose until they have been contacted by their study doctor or designee and told that it is acceptable to dose. Authorization to dose must be documented in the patient's medical records.
~~No action~~</td><td>Monitor every 1 week unless otherwise specified
Obtain additional lab tests (Table 2) if 2 occurrences consecutive or non-consecutive) of platelet count 140K - > 100K/mm^3 or 1 occurrence of platelet count ≤100K/mm^3. Labs only need to be performed once. Labs may be collected over multiple visits, if blood requirements are a concern, as per Investigator discretion
~~Monitor every 2 weeks~~</td></tr>
<tr><td>> 100K/mm^3 ~~- 140K/mm^3~~</td><td>Weekly 300 mg Study Drug administration ~~No action~~</td><td>~~Closer observation~~
~~Monitor every 1 week until stable*~~</td></tr>
<tr><td>~~75K -~~100K/mm^3 - 75K/mm^3</td><td>Permanently reduce dose frequency to 300 mg every 2 weeks ~~or reduce dose to 150 mg weekly~~</td><td>~~Closer observation~~
~~Monitor every 1 week~~</td></tr>
<tr><td>~~50K -~~75K/mm^3 - 50K/mm^3</td><td>If occurs while on dose of 300 mg every 2 weeks ~~or 150 mg every week~~ then permanently discontinue Study Drug, otherwise dose pause.
When platelet count returns to > 100K/mm^3 restart dosing at dose frequency of 300 mg every 2 weeks ~~or 150 mg weekly~~ only if approved by Sponsor Medical Monitor</td><td>~~Closer observation~~
Monitor every 2-3 days until 2 successive values are > 75K/mm^3 then monitor every 1 week~~show improvement~~
Consider discontinuation of antiplatelet agents/NSAIDS/ anticoagulant medication</td></tr>
</table>
</td><td>To provide added patient safety regarding platelet count reductions, ISIS 304801 dose exposure, and treatment recommendations</td></tr>
</table>

<table>
<tr><th>Protocol Section</th><th>Description of Change</th><th>Rationale</th></tr>
<tr>
<td>Section 8.6.3 Stopping Rules for Platelet Count Results
Continued</td>
<td>
Table ~~23~~ Actions in Patients with Low Platelet Count <u>Continued</u>
<table>
<tr><th>Platelet Count on Rx</th><th>Drug Dose</th><th>Monitoring</th></tr>
<tr>
<td>~~25K~~ < 50K/mm^3 or a rate of decline ≥ 50% between two consecutive assessments, irrespective of the platelet level</td>
<td>Permanently discontinue Study Drug</td>
<td>~~Closer observation~~
• Monitor daily until 2 successive values show improvement then monitor every 2-3 days <u>until 2 successive values are > 75K/mm^3 then monitor every 1 week</u> ~~platelet count stable~~
• <u>Patient should be evaluated by a hematologist to provide diagnostic and therapeutic management</u>
• <u>Steroids recommended if platelet count is < 50K/mm^3*. It is strongly recommended that, unless the patient has a medical contraindication to receiving glucocorticoids, the patient receives glucocorticoid therapy to reverse the platelet decline.</u>
• <u>Monitor triglyceride levels weekly and continue AE monitoring during steroid therapy</u>
• Discontinue antiplatelet agents/NSAIDS/anticoagulant medication while platelet count < 50K/mm^3 if possible</td>
</tr>
</table>
</td>
<td>To provide added patient safety regarding platelet count reductions, ISIS 304801 dose exposure, and treatment recommendations</td>
</tr>
</table>

<table>
<tr><th>Protocol Section</th><th>Description of Change</th><th>Rationale</th></tr>
<tr><td>Section 8.6.3 Stopping Rules for Platelet Count Results Continued</td><td>
Table ~~2~~3 Actions in Patients with Low Platelet Count <u>Continued</u>
<table>
<tr><th>Platelet Count on Rx</th><th>Drug Dose</th><th>Monitoring</th></tr>
<tr><td>~~< 25K/mm^3~~</td><td>~~Permanently discontinue Study Drug~~</td><td>~~Closer observation: Monitor daily until 2 successive values show improvement then monitor every 2-3 days until platelet count stable~~
~~Steroids recommended~~**
~~Consider need for hospitalization and referral to hematologist~~
~~Discontinue antiplatelet agents/NSAIDS/anticoagulant medication while platelet count < 50K/mm^3 if possible~~</td></tr>
<tr><td colspan="3">~~*~~ ~~At least 3 consecutive values measured weekly that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3~~
**~~*~~Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (note: may require continuation with oral steroids after methyl prednisolone). In order to reduce the unlikely but potential increased risk of pancreatitis during the period of corticosteroid therapy, triglyceride levels will be monitored weekly, <u>and AE monitoring will continue,</u> during corticosteroid treatment and the laboratory alert will be changed from an increase of 2,000 to 500 mg/dL during that period.</td></tr>
</table>
</td><td>To provide added patient safety regarding platelet count reductions, ISIS 304801 dose exposure, and treatment recommendations</td></tr>
<tr><td>Synopsis
10.1.1 Efficacy Endpoints</td><td>
• Percent change and absolute change from baseline in fasting TG
• Frequency and severity of patient reported abdominal pain during the treatment period
• Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-HDL-C, apoB, HDL-C, apolipoprotein A-1 (apoA-1), VLDL-C, and LDL-C
• Percent change from baseline in fasting total apolipoprotein C-III
• <u>Change in blood viscosity (may be evaluated)</u>
• Quality of Life questionnaires (EQ-5D, SF-36)
• Adjudicated acute pancreatitis event rate
• Other symptoms: eruptive xanthoma, lipemia retinalis
</td><td>To assess potential benefit of ISIS 304801 administration</td></tr>
</table>

Protocol Section	Description of Change	Rationale
Synopsis 10.1.2 Safety Endpoints	• Adverse events including adjudicated events of pancreatitis and MACE • Vital signs and weight • Physical examinations • Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis) • Echocardiography • Electrocardiograms (ECGs) • Use of concomitant medications • MRIs • Platelet aggregation (may be evaluated)	To assess platelet function following ISIS 304801 administration
Appendix A	Removed Week 2.5 CBC with Differential c Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1 week and the result must be reviewed by the Investigator and confirmed to be acceptable before dosing can continue. All platelet count results will be promptly reviewed by the Investigator to determine if the count has met a stopping rule, or the dose reduction rule of 100,000/mm^3, or the ~~and determined not to have met a stopping rule before dosing can continue. If there is no reportable platelet count within 14 days of the last platelet count, the Investigator will contact the patient to hold dosing until a new platelet count is obtained and reviewed. All platelet count results will be promptly reviewed by the Investigator to ensure that the count has not met the stopping rule and to determine whether the rate of decline is suggestive that the patient could be approaching the~~ dose pause rule of 75,000/mm^3. ~~In the event of any platelet count less than 50,000/mm^3 or a rate of decline ≥ 50% between two consecutive assessments, irrespective of the platelet level, then dosing of a patient with Study Drug (ISIS 304801 or placebo) will be stopped permanently.~~ Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor **Added**: Medical History[q] Blood Viscosity[r] Platelet Aggregation[r] Platelet Bound Autoantibodies[r] Archive blood sample for potential gene sequencing related to hypertriglyceridemia (Group 2 if not available from index study)[g] X[s] q Patient charts will be reviewed in order to collect data for events of acute pancreatitis or suspected pancreatitis in the patient's medical history. Chart review may be conducted at any time during the study. These events will be adjudicated in the same manner as for events of pancreatitis during the study r May be done. Blood viscosity and platelet aggregation in volanesorsen-treatment naïve patients only s Platelets are assessed each calendar week, visits do not have specified windows to allow flexibility of scheduling	To provide added patient safety regarding platelet count reductions, ISIS 304801 dose exposure, and treatment recommendations Medical history, blood viscosity and potential gene sequencing to assess potential benefit of ISIS 304801 administration Platelet aggregation to assess platelet function following ISIS 304801 administration

Protocol Section	Description of Change	Rationale
Appendix B	**Added**: Troponin I[2] CK-MB[2] Platelet Bound Autoantibodies[3] Blood Viscosity[3] Platelet Aggregation[3] 2 All abnormal troponin samples will be rerun at the central laboratory and also analyzed for CK-MB 3 May be done	To provide added patient safety regarding platelet count reductions, ISIS 304801 dose exposure, and treatment recommendations Blood viscosity to assess potential benefit of ISIS 304801 administration Platelet aggregation to assess platelet function following ISIS 304801 administration

PROTOCOL SYNOPSIS

Protocol Title	An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Study Phase	3
Indication	Familial Chylomicronemia Syndrome
Study Objectives	To evaluate the safety and efficacy of dosing and extended dosing with volanesorsen (volanesorsen sodium 300 mg) in patients with FCS
Study Design	This is a multi-center open-label study of: Group 1: ISIS 304801-CS6 (index study) roll over FCS patients Group 2: ISIS 304801-CS16 (index study) roll over FCS patients All patients will receive volanesorsen 300 mg once per week for 52 weeks. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period. Following the Week 52 visit, patients will enter an at least 26-week post-treatment evaluation period or will participate in an expanded access program pending approval by the IRBs/IEC, and the appropriate regulatory authorities.
Number of Patients	Up to approximately 70 patients dosed
Study Population	Inclusion Criteria: 1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law 2. Age ≥ 18 years at time of informed consent 3. Groups 1 and 2: Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement. Group 2: Patients who enrolled in ISIS 304801-CS16 must also meet the following criteria in order to enter into the open-label study: a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L) b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) supported by documentation of at least 1 of the following: • Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1) • Post heparin plasma LPL activity of ≤ 20% of normal in medical history. Note: testing of LPL activity should not be performed to confirm eligibility for the study c. Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 index study 4. Able and willing to participate in a 78-week study

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	Inclusion Criteria: *Continued* 5. Satisfy 1 of the following: a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved), abstinent*, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration b. Males: Surgically sterile, abstinent* or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration * Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception Exclusion Criteria: 1. Diabetes mellitus with any of the following: a. Newly diagnosed within 12 weeks of Qualification b. HbA1c ≥ 9.0% at Qualification c. Recent change in anti-diabetic pharmacotherapy (change in dosage or addition of new medication within 12 weeks of Qualification [with the exception of ± 10 units of insulin]) d. Anticipated need to change dose or type of medication during the treatment period of the Study (with the exception of ± 10 units of insulin) e. Current use of GLP-1 agonists 2. Severe hypertriglyceridemia other than due to familial chylomicronemia syndrome 3. Active pancreatitis within 4 weeks prior to Qualification 4. History within 6 months of Qualification of acute or unstable cardiac ischemia (myocardial infarction, acute coronary syndrome, new onset angina), stroke, transient ischemic attack or unstable congestive cardiac failure requiring a change in medication or major surgery within 3 months of Qualification

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	Exclusion Criteria: *Continued* 5. Any of the following laboratory values at Qualification a. Hepatic: • Total bilirubin > upper limit of normal (ULN), unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL • ALT > 2.0 x ULN • AST > 2.0 x ULN b. Renal: • Persistently positive (2 out of 3 consecutive tests ≥ 1+) for protein on urine dipstick. In the event of a positive test eligibility may be confirmed by a quantitative total urine protein measurement of < 500 mg/24 hrs • Persistently positive (2 out of 3 consecutive tests ≥ trace positive) for blood on urine dipstick. In the event of a positive test eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field • Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault < 50 mL/min (MDRD or CKD-EPI formulas can be used instead of Cockcroft-Gault for estimation of GFR in patients with low body weight after discussion with Sponsor Medical Monitor) c. Cardiac Troponin I > ULN at Qualification d. LDL-C > 130 mg/dL at Qualification e. Any other laboratory abnormalities which, in the opinion of the Investigator or the Sponsor, would make the patient unsuitable for inclusion 6. Uncontrolled hypertension (BP > 160/100 mm Hg) 7. History of thrombocytopenia (platelet count < 100,000/mm^3) or bleeding diathesis or coagulopathy or clinically-significant abnormality in coagulation parameters at Qualification 8. History of heart failure with NYHA greater than Class II 9. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1 10. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B 11. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated 12. Treatment with another investigational drug, biological agent, or device within 1 month of Qualification, or 5 half-lives of investigational agent, whichever is longer 13. Unwilling to comply with lifestyle requirements (Section 6.3)

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	Exclusion Criteria: *Continued* 14. Use of any of the following: a. Statins, omega-3 fatty acids (prescription and OTC), or fibrates unless on a stable dose for at least 3 months prior to Qualification and dose and regimen expected to remain constant during the treatment period. Patients taking OTC omega-3 fatty acids should make every effort to remain on the same brand throughout the study b. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to Qualification c. Systemic corticosteroids or anabolic steroids within 6 weeks prior to Qualification unless approved by the Sponsor Medical Monitor d. Atypical antipsychotic medications (e.g., olanzapine and clozapine) unless on a stable dose for at least 3 months prior to Qualification and dose and regimen expected to remain stable throughout the study e. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to Qualification and dose and regimen expected to remain constant during the treatment period f. Glybera gene therapy within 2 years prior to Qualification g. Oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, and apixaban) unless on a stable dose for at least 4 weeks prior to Qualification and regular clinical monitoring is performed h. Tamoxifen, estrogens or progestins unless on a stable dose for at least 4 months prior to Qualification and dose and regimen expected to remain constant during the treatment period i. Plasma apheresis within 4 weeks prior to Qualification or planned during the study j. Prior exposure to ISIS 304801 k. Any other medication unless stable at least 4 weeks prior to Qualification (Occasional or intermittent use of over-the-counter medications will be allowed at Investigator's discretion) 15. Blood donation of 50 to 499 mL within 30 days of Qualification or of > 499 mL within 60 days of Qualification 16. Known hypersensitivity to any of the excipients of the Study Drug (ISIS 304801 or placebo) 17. Have any other conditions, including new or worsening of existing condition, which, in the opinion of the Investigator or the Sponsor would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the study
Treatment Group	Volanesorsen 300 mg once per week
Study Drug Administration	Volanesorsen will be administered as subcutaneous (SC) injections.
Dose Adjustments	Dose adjustments, including dose interruptions and/or decreasing the dose frequency will be allowed for safety or tolerability after consultation with the Sponsor Medical Monitor.

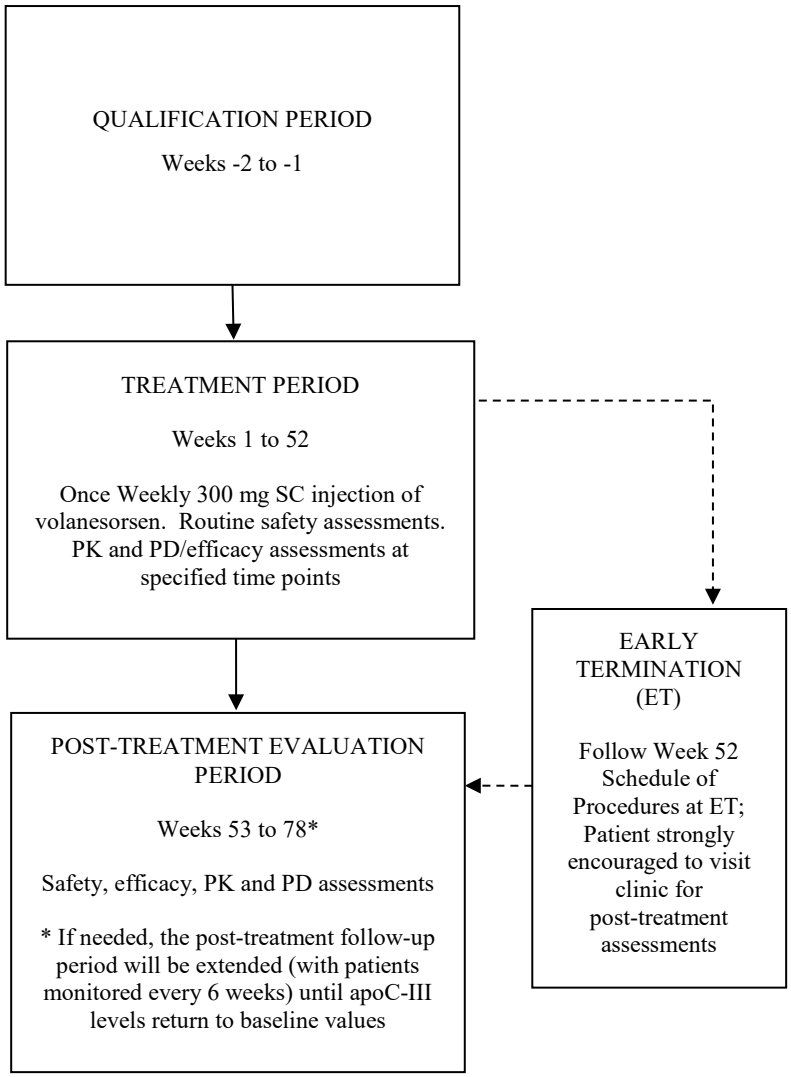
PROTOCOL SYNOPSIS *Continued*

Rationale for Dose and Schedule Selection	The dose of 300 mg once weekly was chosen for the double-blinded placebo-controlled Phase 3 index studies (ISIS 304801-CS6 and ISIS 304801-CS16) based on the pharmacodynamic and safety analysis of the Phase 2 studies (Section 2.4) which included a subset of patients with FCS. The same dose of 300 mg once weekly will be used in this open-label study of FCS patients.
Study Visit Schedule and Procedures	The study for an individual patient will generally consist of the following periods: • A qualification period of up to 2 weeks (unless approved by the Sponsor). Please refer to Section 4.1 and Appendix A • A 52-week treatment period during which volanesorsen will be administered as a once weekly SC injection • An at least 26-week post-treatment evaluation period The patients, Investigators, study staff, and the Sponsor will remain blinded to lipid data through the last patient's Week 13 visit of the open-label study or until results from the database locks for the ISIS 304801-CS6 and ISIS 304801-CS16 index studies becomes available, whichever comes first. Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), adverse events (AE), concomitant medication/procedure information, lipid panel, blood viscosity, volanesorsen plasma concentrations, immunogenicity (IM) testing, platelet aggregation, liver/spleen magnetic resonance imaging (MRI), ECGs, echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Dietary counseling will be repeated at intervals throughout the treatment and follow-up period and a daily food/drink diary will be completed for the week prior to each quarterly visit by each patient. Following the Week 52 visit, patients will enter an at least 26-week post-treatment evaluation period or will participate in an expanded access program pending approval by the IRBs/IEC, and the appropriate regulatory authorities.
Safety and Tolerability Evaluations	Overall safety and tolerability of volanesorsen will be assessed by determining the incidence and severity of adverse and serious adverse events (including independently adjudicated events of acute pancreatitis and MACE), withdrawals due to adverse events, and changes in laboratory and other safety parameters.

PROTOCOL SYNOPSIS *Continued*

Planned Analyses	Safety Endpoints: • Adverse events including adjudicated events of acute pancreatitis and MACE • Vital signs and weight • Physical examinations • Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis) • Echocardiography • Electrocardiograms (ECGs) • Use of concomitant medications • MRIs • Platelet aggregation (may be evaluated) Efficacy Endpoints: • Percent change and absolute change from baseline in fasting TG • Frequency and severity of patient reported abdominal pain during the treatment period • Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-high-density lipoprotein-cholesterol (non-HDL-C), apolipoprotein B [apoB], high-density lipoprotein-cholesterol (HDL-C), apolipoprotein A-1 [apoA-1], very-low-density lipoprotein-cholesterol (VLDL-C), and LDL-C • Percent change from baseline in fasting total apolipoprotein C-III (apoC-III) • Change in blood viscosity (may be evaluated) • Quality of Life questionnaires (EQ-5D, SF-36) • Adjudicated acute pancreatitis event rate • Other symptoms: eruptive xanthoma, lipemia retinalis
Pharmacokinetic Evaluations	Plasma samples will be taken from all patients for the measurement of volanesorsen as follows: trough levels (pre-dose) throughout treatment and post-treatment levels during the post-treatment follow-up period. In a subset of patients, more frequent assessment of plasma concentrations of volanesorsen will be performed to determine volanesorsen pharmacokinetic parameters. Plasma sample collection time points are detailed in Appendix A and Appendix C.
Statistical Considerations	No sample size calculations were performed as this is an open-label study.
Sponsor	Ionis Pharmaceuticals, Inc.
Collaborator	Akcea Therapeutics

STUDY DESIGN AND TREATMENT SCHEMA



STUDY GLOSSARY

Abbreviation/Acronym	Definition
ADA	anti-drug antibody
AE	adverse Event
ALP	alkaline Phosphatase
ALT	alanine Aminotransferase
ANA	antinuclear Antibody
apoA-1	apolipoprotein A-1
apoB	apolipoprotein B
apoC-III	apolipoprotein C-III
apoE	apolipoprotein E
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
CBC	complete blood count
C_{max}	maximum observed drug concentration
CRF	case report form
DNA	deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
ET	early termination
FAS	full analysis set
FCS	Familial Chylomicronemia Syndrome
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
GPIHBP1	Glycosylphosphatidylinositol-anchored HDL-binding Protein 1
HAPI	Heritability and Phenotype Intervention
HbA1c	Glycated Hemoglobin
HDL	High-Density Lipoprotein
HDL-C	High-Density Lipoprotein-Cholesterol
hsCRP	High-sensitivity C-reactive protein
ICH	International Conference on Harmonization
IDL	Intermediate density lipoprotein
IEC	Independent Ethics Committee
IM	immunogenicity
Index Studies	ISIS 304801-CS6 and ISIS 304801-CS16

STUDY GLOSSARY *Continued*

Abbreviation/Acronym	Definition
INR	International Normalized Ratio
IRB	Institutional Review Board
IXRS	Interactive Voice/Web-Response System
LDL	Low-Density Lipoprotein
LDL-C	Low-Density Lipoprotein-Cholesterol
LMF1	Lipase Maturation Factor 1
LPL	Lipoprotein Lipase
MACE	Major Acute Cardiovascular Event
MOE	2′-*O*-(2-methoxyethyl)
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NCS	not clinically-significant
NOAEL	No-Observed-Adverse-Effect Level
non-HDL-C	Non-High-Density Lipoprotein-Cholesterol
OTC	over the counter
PFS	prefilled syringe
PD	pharmacodynamic
PK	pharmacokinetic
PPS	per protocol set
PT	prothrombin time
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SUSAR	suspected unexpected serious adverse reaction
T2DM	type 2 diabetes mellitus
T_{max}	time to maximal concentration
TG	triglycerides
Treatment-emergent	occurring after first dose of Study Drug
TRL	Triglyceride-Rich Lipoproteins
ULN	upper limit of normal
VLDL	Very-Low-Density Lipoprotein
VLDL-C	Very-Low-Density Lipoprotein-Cholesterol
VLDL-TG	Lipoprotein-Triglyceride
WMA	World Medical Association

1. OBJECTIVES

The objective of the study is to evaluate the safety and efficacy of dosing and extended dosing with volanesorsen in patients with familial chylomicronemia syndrome.

2. BACKGROUND AND RATIONALE

2.1 Overview of Disease

Familial Chylomicronemia Syndrome (FCS) is an inherited disease characterized by severe hypertriglyceridemia and chylomicronemia, and risk or history of pancreatitis. It is a rare autosomal recessive disease that can be diagnosed either in childhood or adulthood.

Fasting plasma triglyceride (TG) levels in FCS patients are typically 10-fold to 100-fold above normal (1,500 to 15,000 mg/dL), despite extreme dietary fat restriction (20 g or approximately 15-20% of daily calorie intake) (Brunzell 1999-2011). Patients with FCS often present in infancy or childhood with frequent and severe abdominal pain, repetitive colicky pain, repeated episodes of potentially fatal acute pancreatitis, and failure to thrive (Brunzell 1999-2011; Tremblay et al. 2011). Physical examination frequently reveals eruptive xanthomas, lipemia retinalis and hepatosplenomegaly, and plasma from patients appears lactescent, interfering with determination of other laboratory parameters (Tremblay et al. 2011).

Patients with fasting triglyceride levels > 10 mmol/L probably have a component of chylomicronemia. Clinical diagnosis would include evidence of clinical features of chylomicronemia syndrome and secondary causes such as uncontrolled type 1 or type 2 diabetes mellitus (T2DM), hypothyroidism, poor diet, alcohol use, nephrotic syndrome or use of associated medications should be ruled out. The diagnosis of FCS may be made more specifically by genotyping or confirmation of very low or absent lipoprotein lipase (LPL) enzyme activity in post heparin plasma (Brunzell 1999-2011).

Patients with FCS carry a heavy burden of medical complications, the most serious, as described above, being an extreme risk of recurrent and potentially fatal pancreatitis. Due to the recurrent episodes of acute pancreatitis, these patients may also develop chronic pancreatitis and signs of exocrine or endocrine pancreatic insufficiency, including diabetes mellitus (Gaudet et al. 2013). While the pathophysiology underlying chylomicron-related pancreatitis has not been completely elucidated, 1 hypothesis is that large chylomicrons lodged in pancreatic capillaries are exposed to pancreatic lipase, with the subsequent release of free fatty acids through the hydrolysis of chylomicron-associated TGs. High concentrations of free fatty acids are thought to damage pancreatic cells leading to emergent pancreatitis (Yang et al. 2009; Berglund et al. 2012).

The etiology of extreme hypertriglyceridemia in FCS is considered to be ineffective triglyceride clearance, due to an extremely low level of LPL activity. LPL normally functions to hydrolyze triglycerides (TG) in chylomicrons along the luminal surface of capillaries, mainly in heart, skeletal muscle, and adipose tissue, promoting triglyceride clearance from the circulation. LPL is regulated by a number of key genes, and loss-of-function mutations in one of these genes, or the LPL gene itself, results in FCS (Surendran et al. 2012). In addition to loss of function mutations, null mutations, and nonsense mutations in the LPL gene, other genes currently identified in FCS patients, and known to directly influence LPL activity include: apolipoprotein C-II (APOC2) a cofactor for LPL (Schuster et al. 2011); apolipoprotein A-V

(APOA5) an enhancer of LPL activity (Schaap et al. 2004); lipase maturation Factor 1 (LMF1), a transmembrane protein involved in LPL maturation (Doolittle et al. 2009); glycosylphosphatidylinositol-anchored HDL-binding protein 1 (GPIHBP1), a capillary endothelial cell protein that provides a platform for LPL-mediated processing of chylomicrons (Beigneux et al. 2007).

2.2 Therapeutic Rationale

Apolipoprotein C-III (ApoC-III), a key regulator of plasma triglyceride levels, is a 79 amino acid glycoprotein synthesized principally in the liver (Ooi et al. 2008; Figure 1). ApoC-III is a major regulator of lipoprotein metabolism and plays a pivotal role in regulating plasma TG levels (Chan et al. 2008). It is a component of triglyceride-rich lipoproteins (TRLs) and a potent inhibitor of LPL (Lemieux et al. 2003). At higher concentrations apoC-III also inhibits hepatic lipase activity (Kinnunen and Ehnolm 1976), an enzyme which plays an important role in the conversion of dense very-low-density lipoprotein (VLDL) to intermediate density lipoprotein (IDL) and to LDL (Mendivil et al. 2010), as well as in the remodeling of HDL (Brown et al. 2010). In addition, increased apoC-III content adversely affects apoE-mediated hepatic uptake of TG-rich remnants (Mann et al. 1997). Thus, elevated plasma apoC-III levels are associated with impaired hydrolysis and retarded clearance of TG-rich particles, resulting in the accumulation of lipoprotein-triglyceride (VLDL-TG) and chylomicrons in plasma and the development of hypertriglyceridemia (Ito et al. 1990).

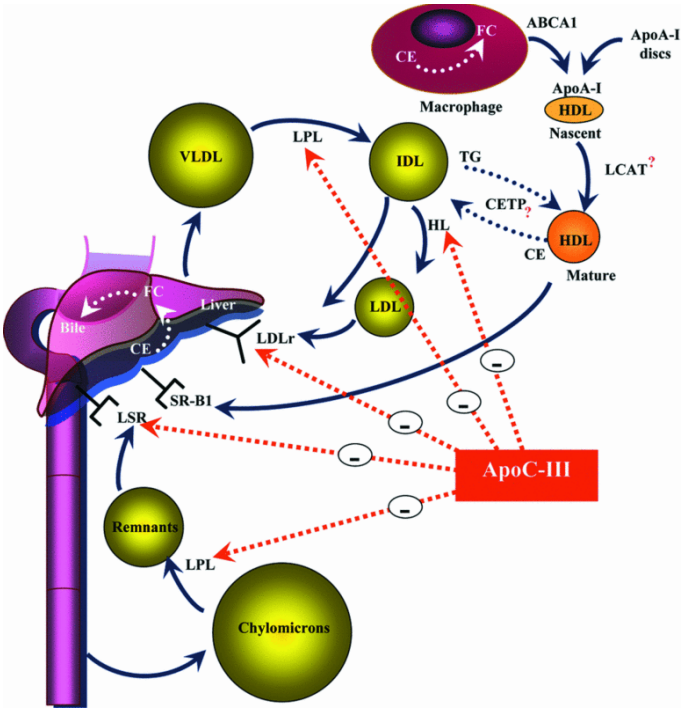


Figure 1 ApoC-III Regulates Lipoprotein Metabolism by Multiple Mechanisms

From Ooi et al. 2008; ABCA1 = ATP-binding cassette A1, apo = apolipoprotein, CE = cholesterol ester, CETP = cholesterol ester transfer protein, FC = free cholesterol, HDL = high-density lipoprotein, HL = hepatic lipase, IDL = intermediate-density lipoprotein, LCAT = lecithin cholesterol acyltransferase, LDL = low-density lipoprotein, LDLr = LDL receptor, LPL = lipoprotein lipase, LSR = lipolysis-stimulated receptor, SR-B1 = scavenger receptor B-1, TG = triglyceride, VLDL = very low-density lipoprotein.

Mechanistically, FCS is primarily a consequence of ineffective clearance of TRL. ApoC-III is a prominent component of TRL (e.g., VLDL and chylomicrons). In addition to its role in inhibiting LPL, apoC-III inhibits TRL remnant (TG-depleted remnant lipoprotein) uptake by hepatic lipoprotein receptors by steric inhibition of the interaction of apoE with these receptors.

Human genetic data have demonstrated positive phenotypic associations with loss (e.g., null or nonsense mutations) and negative effects with gain of function mutations (Atzmon et al. 2006; Pollin et al. 2008; Petersen et al. 2010). A novel nonsense mutation in the apoC-III gene was identified in the heritability and phenotype intervention (HAPI) heart study in Old Order Amish that results in lower plasma apoC-III and TG levels and lower LDL-C, increased HDL-C and reduced atherosclerosis (Pollin et al. 2008). In another study involving a group of 214 Ashkenazi Jews of advanced age (had passed or nearly reached 100 years of age), genotype analysis revealed a polymorphism in the apoC-III gene (APOC3-641CC genotype) with a clear pattern of age-dependent frequency that was associated with significantly lower levels of apoC-III protein, a favorable lipoprotein profile and increased longevity (Atzmon et al. 2006). In contrast to the Amish and Ashkenazi apoC-III polymorphisms associated with lower plasma TG, apoC-III polymorphisms associated with higher plasma TG have also been recently described (Petersen et al. 2010). In a cohort of lean (mean body mass index [BMI] = 24.7 ± 3.6 kg/m^2) Asian Indians, carriers of apoC-III variant alleles (C-482T, T-455C, or both) were noted to have significantly higher plasma apoC-III and TG levels, and decreased ability to clear postprandial plasma TG from the circulation. Taken together, the available data strongly support the development of a therapy that reduces plasma apoC-III levels in order to reduce the very high circulating triglyceride and chylomicron levels that are accompanied by increasing risk for acute pancreatitis.

Given the profound reductions in TGs observed with volanesorsen treatment in FCS patients who have no detectable LPL activity (See Section 2.3.4), and the mechanistic data available to date on apoC-III function, potential mechanisms that explain how apoC-III inhibition results in triglyceride reduction in FCS patients include: (1) enhancing the very small residual amounts of LPL activity that these patients may have, below the limit of detection of the assay in many cases (2) potentially enhanced activity of other lipases also involved in the metabolism and breakdown of TGs, such as hepatic lipase or endothelial lipase (Kinnunen and Ehnolm 1976), and (3) apoC-III interaction with Apolipoprotein E (apoE), an important factor in liver reuptake of lipid particles by blocking apoE-mediated uptake of lipid particles in the liver (Breyer et al. 1999), and therefore, reducing apoC-III might enhance apoE-mediated uptake of lipid particles. Volanesorsen-mediated reduction of apoC-III could be contributing to one or all of these mechanisms resulting in the observed potent and sustained reductions in TG.

Through a novel apoC-III lowering mechanism of action, volanesorsen may provide the potential to manage triglyceride levels in FCS patients.

2.3 Volanesorsen

2.3.1 Mechanism of Action

Volanesorsen is a second-generation antisense oligonucleotide (ASO) drug targeted to human apoC-III. It is complementary to a region within the 3′ untranslated region of the apoC-III messenger ribonucleic acid (mRNA) and binds to the mRNA by Watson and Crick base pairing.

The hybridization (binding) of volanesorsen to the cognate mRNA, results in the RNase H1-mediated degradation of the apoC-III mRNA, thus preventing production of the apoC-III protein. Maximal antisense-mediated reduction of target mRNA levels is typically greater than 90% of control levels in sensitive tissues (Crooke and Bennett 1996; Zhang et al. 2010). Furthermore, reduction in target mRNA levels using this approach correlates directly with a subsequent reduction in target protein levels.

2.3.2 Chemistry

Chemically, volanesorsen is a synthetic oligomer of 20 nucleotides (i.e., a 20-mer) that are connected sequentially by phosphorothioate linkages. The nucleotide sequence of volanesorsen (Figure 2) is complementary to a 20-nucleotide stretch within the 3′ untranslated region of the apoC-III mRNA transcript at base position 489-508. Structurally, the oligonucleotide has 3 regions. Two (2) of them, the 5 nucleotides at the 5′ end and the 5 nucleotides at the 3′ end, are composed of 2′-*O*-(2-methoxyethyl) (MOE)-modified ribonucleotides. These MOE-modified nucleotides confer (1) increased affinity to the target mRNA (Altmann et al. 1996; McKay et al. 1999), (2) increased resistance to exonucleases and endonucleases (thereby increasing stability in tissue) (Geary et al. 2003), and (3) amelioration of some of the high dose toxicities thereby resulting in an improved safety profile compared to first generation antisense drugs containing phosphorothioate modified oligodeoxynucleotides (DNA) (Henry et al. 2000). The third region, the central portion of the oligonucleotide, is composed of 10 oligodeoxynucleotides. This chimeric design is called a MOE-Gapmer, and volanesorsen employs this chimeric structure to enable use of the RNase H1-mechanism for antisense activity. This is because while the 2′-MOE modification confers increased stability and affinity, it does not support RNase H1 catalysis of RNA hybridized to 2′-MOE-modified nucleotides (McKay et al. 1999). This is caused by conformational changes induced in the heteroduplex by 2′-alkoxy:RNA hybrids that are not recognized by RNase H1 enzymes (Inoue et al. 1987; Monia et al. 1993). By limiting the 2′-MOE modification to nucleotides flanking the phosphorothioate oligodeoxynucleotide core, the beneficial attributes of the 2′-MOE chemistry are preserved while also retaining RNase H1 recognition.

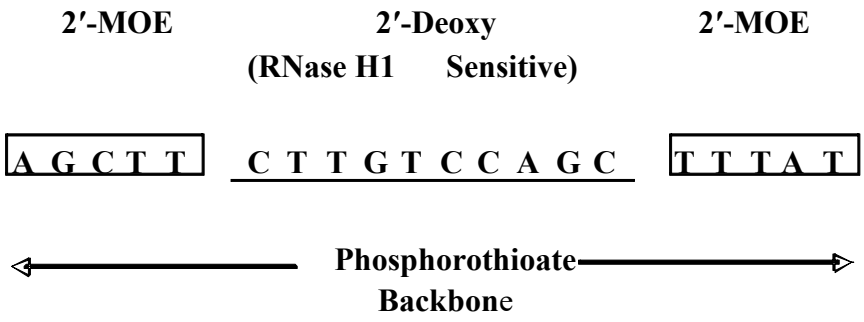


Figure 2 Design of Chimeric 2′-MOE Phosphorothioate Oligonucleotides (MOE-Gapmer). The sequence of volanesorsen is shown

2.3.3 Preclinical Experience

Inhibition of apoC-III using volanesorsen has been shown to potently reduce hepatic apoC-III mRNA as well as plasma apoC-III protein and TG in a dose- and time-dependent fashion in several species, including human apoC-III transgenic mice, and other rodent and monkey models. Treatment with volanesorsen also resulted in reduced VLDL and chylomicron TG and reduced postprandial TG in hypertriglyceridemic monkeys (Graham et al. 2013).

The pharmacokinetics (PK) and toxicity of volanesorsen have been assessed in mice, rats, and cynomolgus monkeys. General toxicity studies with volanesorsen for up to 39 weeks of treatment followed by up to a 20-week recovery period are complete. The preclinical toxicology program for volanesorsen consists of single dose safety pharmacology studies in the monkey (cardiovascular) and mouse (neurobehavioral and pulmonary assessment studies), *in vitro* and *in vivo* genetic toxicity assessment, repeat dose fertility and/or developmental reproductive toxicology studies in the mouse and rabbit and evaluation in the *in vitro* human Ether-á-go-go-related gene (hERG) assay.

Volanesorsen treatment-related findings in mice and monkeys were generally consistent with those expected for the 2′-MOE-class of ASOs. Treatment-related findings included effects consistent with drug accumulation in tissues in rodents and monkeys, species-dependent proinflammatory response in rodents and monkeys and complement activation and reductions in platelet counts in the monkey. In the mouse and monkey general toxicity studies, reduction of hepatic apoC-III mRNA (> 75%) was not associated with any findings that could be considered related to the pharmacologic inhibition of apoC-III for up to 39 weeks of treatment.

The long-term, chronic toxicology studies in rodents with volanesorsen produced a significant proinflammatory response that led to subsequent effects on the heart at high doses. The rodent species are most sensitive to the proinflammatory effects of antisense molecules. Importantly, these effects on the heart were not observed in the monkey chronic toxicity studies even at the highest doses tested where drug exposure was higher than that in rodents.

Because these changes were not observed in monkeys, the findings in the heart are considered to be rodent-specific and not relevant to humans. Nevertheless, such effects will be monitored by measurement of echocardiograms that will be included in this clinical study.

Volanesorsen caused no untoward effects in safety pharmacology studies (*in vitro* and *in vivo*) and was non-genotoxic (*in vitro* and *in vivo*). Volanesorsen had no effects on fertility or embryo/fetal development in the mouse or rabbit reproductive toxicity studies. In these studies, volanesorsen was detected in placental tissue but not in fetal tissue indicating that little, if any, drug was able to cross the placenta to reach the fetus. Reduction of apoC-III mRNA (64% in males and 47% in females) also did not affect fertility or cause untoward effects on embryo/fetal development in mice.

Detailed information concerning the preclinical studies conducted with volanesorsen can be found in the volanesorsen Investigator's Brochure.

2.3.4 Clinical Experience

Detailed information concerning the clinical studies conducted with volanesorsen can be found in the volanesorsen Investigator's Brochure. A summary is included below.

Volanesorsen has been evaluated in one Phase 1 study and two Phase 2 studies, all double blinded and placebo controlled. The total exposures comprise 99 patients and healthy volunteers administered volanesorsen from 50 to 400 mg subcutaneously up to 3 months (compared to 37 administered placebo).

All clinical trials of volanesorsen have shown large and clinically meaningful reductions in fasting plasma apoC-III and TG (~80% and 70%, respectively, mean reduction from baseline with 300 mg dose) with a very high degree of consistency of response between the different patient groups. This includes healthy volunteers, patients with moderate to severe hypertriglyceridemia not on background TG-lowering therapy, patients with moderate to severe hypertriglyceridemia on a background stable fibrate therapy (Gaudet et al. 2015), patients with FCS, and patients with T2DM.

In a Phase 2 study, 3 patients with FCS were treated with 300 mg/wk volanesorsen in an open-label fashion. These patients had a mean baseline fasting TG level of 1,844 mg/dL and all 3 patients achieved TG levels below or close to 500 mg/dL during the dosing period out to Day 92 (Figure 3). Two (2) of the FCS patients had an absolute reduction in fasting TG in excess of 1,500 mg/dL (Gaudet et al. 2014).

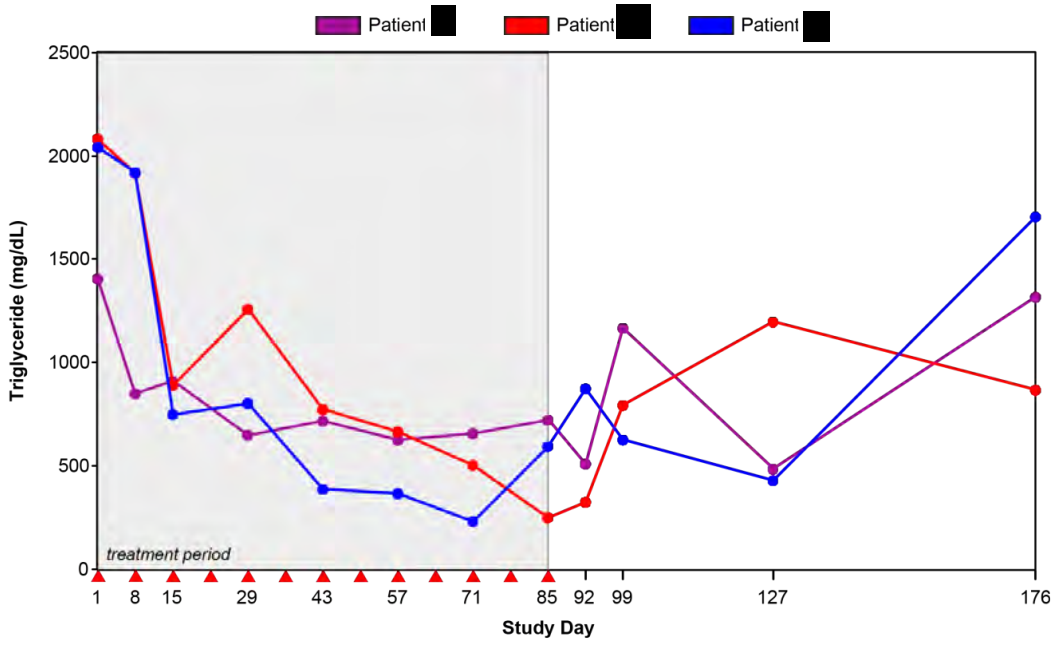


Figure 3 Fasting Triglycerides in Patients with FCS Treated with Volanesorsen

In clinical studies conducted to date volanesorsen has been well-tolerated and has shown a favorable safety profile. There has been no clinical or laboratory evidence of drug-drug interactions.

In the completed studies there have been no volanesorsen associated laboratory abnormalities suggestive of an effect on the renal (serum creatinine, proteinuria) or hepatic systems (alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin). In Phase 2 studies, there was a mild decrease of platelet count associated with volanesorsen administration that recovered in the post-treatment period and was not associated with platelet-related adverse events (AEs). In the blinded ongoing clinical trials of ISIS 304801, 2 patients of 142 dosed (as of February 29, 2016) had a decrease in platelet count to less than 50,000/mm^3 in the absence of major bleeding or clinically-relevant non-major bleeding and had Study Drug paused as per the monitoring and stopping rules for platelet counts (Section 8.6.3). Platelet counts recovered following suspension of dosing.

The most frequently observed AEs with volanesorsen were local reactions at the injection site. Local cutaneous reactions at the injection site defined as those events presenting as either pain, tenderness, erythema, pruritus or swelling occurring on the day of injection and persisting for at least 2 days were infrequent (~15% of injections), were almost always mild, resolved spontaneously, were non-progressive, and were not associated with systemic sequelae.

2.4 Rationale for Dose and Schedule of Administration

The dose and schedule selected for this study is 300 mg per week for 52 weeks. The dose of 300 mg per week is supported by both the cumulative nonclinical data available to date and the Phase 2 clinical data. In nonclinical studies, volanesorsen treatment-related effects in rodents and monkeys were consistent with drug accumulation in tissues and also include species-specific proinflammatory responses. In the monkey, the No-Observed-Adverse-Effect Level (NOAEL) was defined by the cumulative clinical pathology results and histopathology data which provide an adequate clinical margin. No nonclinical findings were considered to be related to the pharmacologic inhibition of apoC-III.

The safety data to date suggest that volanesorsen has been well-tolerated at dose levels up to 300 mg in patients with high triglycerides (including type 2 diabetes patients and administration in combination with fibrates and statins) with the most common AEs being local to the injection site and predominantly mild. A pooled analysis of safety for the Phase 2 studies did not demonstrate any clear difference in safety or tolerability between the different doses tested (100 mg, 200 mg, and 300 mg per week for 13 weeks).

Analysis of the cohorts in which volanesorsen was studied at different doses demonstrates dose-dependent pharmacology with respect to pharmacodynamic (PD) effect on the target, apoC-III, with a clear difference in the TG-lowering effect between the different doses in the 100 mg to 300 mg dose range as compared to placebo.

In addition to the nonclinical and clinical experience of volanesorsen, the dose and schedule of administration is supported by the preclinical and clinical safety experience of several other 2′-MOE-modified ASOs that have been safely administered intravenously and subcutaneously in multiple clinical studies at doses up to 1000 mg and for treatment durations that exceed 24 months (Santos et al. 2015).

3. EXPERIMENTAL PLAN

3.1 Study Design

This is an open-label study of:

Group 1: ISIS 304801-CS6 (index study) roll over FCS patients

Group 2: ISIS 304801-CS16 (index study) roll over FCS patients

Up to approximately 70 patients will receive 300 mg once weekly volanesorsen for 52 weeks.

Following the Week 52 visit, patients enter an at least 26-week post-treatment evaluation period or will participate in an expanded access program pending approval by the IRBs/IEC, and the appropriate regulatory authorities.

3.2 Number of Study Centers

This study will be conducted at multiple centers worldwide.

3.3 Number of Patients

Up to approximately 70 patients will be dosed.

3.4 Overall Study Duration and Follow-up

The Study will consist of the following periods:

3.4.1 Qualification

A qualification period of up to 2 weeks (unless approved by the Sponsor) is given to complete qualification assessments outlined in the Schedule of Procedures. Please refer to Section 4.1 and Appendix A.

3.4.2 Treatment

The treatment period is 52 weeks. Eligible patients will report to the Study Center for assessments at specified intervals throughout the 52-week treatment period as detailed in the Schedule of Procedures (Appendix A). During the treatment period, volanesorsen is administered by SC injection once weekly.

3.4.3 Post-Treatment

The post-treatment evaluation period is at least 26 weeks and consists of at least 9 Study Center visits on Weeks 53, 54, 55, 56, 57, 58, 65, 71, and 78 (Weeks 53, 54, 55, 56, 57, 58, and 71 may be conducted by a home healthcare nurse).

3.5 End-of-Study

The End-of-Study is last patient, last visit.

3.6 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will review (as needed) safety, tolerability and efficacy data collected on volanesorsen during this study. Based on its ongoing assessment of the safety and tolerability of volanesorsen, the DSMB will provide

recommendations to the Sponsor for modifying, stopping or continuing the study as planned. Details on the safety assessments, frequency of review and meeting schedules are outlined in the DSMB Charter and/or the statistical analysis plan (SAP).

4. PATIENT ENROLLMENT

4.1 Qualification

Before patients may be enrolled into the study, the Sponsor requires a copy of the Study Center's written independent ethics committee/institutional review board (IEC/IRB) approval of the protocol, informed consent form, and all other patient information.

Patients or their legally acceptable representatives must sign the consent form before any study-specific procedures or evaluations related to this open-label study are performed.

During the qualification period, the eligibility of the patient to enroll in the open-label study will be determined. Final assessments from the ISIS 304801-CS6 or ISIS 304801-CS16 studies may be used for qualification. A period of up to 2 weeks after completion of the ISIS 304801-CS6 or ISIS 304801-CS16 index studies (unless approved by the Sponsor) is given to complete qualification. Qualified patients will retain the unique patient identification number that was assigned to them during the ISIS 304801-CS6 or ISIS 304801-CS16 index studies. The patient identification number will be used to identify the patient throughout the extension trial and must be used on all study documentation related to that patient. The patient identification number must remain constant throughout the extension trial.

4.2 Enrollment

Patients will be enrolled into the treatment phase of the study after all qualification assessments have been completed and after the Investigator has verified that they are eligible per criteria in Sections 5.1 and 5.2. No patient may begin treatment prior to enrollment.

Eligible patients will be enrolled using an Interactive Voice/Web-Response System (IXRS).

5. PATIENT ELIGIBILITY

To be eligible to participate in this study candidates must meet the following eligibility criteria within 2 weeks of Study Day 1, or at the time point specified in the individual eligibility criterion listed.

5.1 Inclusion Criteria

1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law
2. Age ≥ 18 years at time of informed consent
3. Groups 1 and 2: Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement.

   Group 2: Patients who enrolled in ISIS 304801-CS16 must also meet the following criteria in order to enter into the open-label Study:

a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L)

b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) supported by documentation of at least 1 of the following:

- Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1)
- Post heparin plasma LPL activity of ≤ 20% of normal in medical history. Note: testing of LPL activity should not be performed to confirm eligibility for the study.

c. Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 index study

4. Able and willing to participate in a 78-week study
5. Satisfy 1 of the following:

a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved), abstinent*, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration.

b. Males: Surgically sterile, abstinent* or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration.

* Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception

5.2 Exclusion Criteria

1. Diabetes mellitus with any of the following:

a. Newly diagnosed within 12 weeks of Qualification

b. HbA1c ≥ 9.0% at Qualification

c. Recent change in anti-diabetic pharmacotherapy (change in dosage or addition of new medication within 12 weeks of Qualification [with the exception of ± 10 units of insulin])

d. Anticipated need to change dose or type of medication during the treatment period of the Study (with the exception of ± 10 units of insulin)

e. Current use of GLP-1 agonists

2. Severe hypertriglyceridemia other than due to familial chylomicronemia syndrome
3. Active pancreatitis within 4 weeks prior to Qualification
4. History within 6 months of Qualification of acute or unstable cardiac ischemia (myocardial infarction, acute coronary syndrome, new onset angina), stroke, transient ischemic attack or unstable congestive cardiac failure requiring a change in medication or major surgery within 3 months of Qualification
5. Any of the following laboratory values at Qualification

   a. Hepatic:

      - Total bilirubin > upper limit of normal (ULN), unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL
      - ALT > 2.0 x ULN
      - AST > 2.0 x ULN

   b. Renal:

      - Persistently positive (2 out of 3 consecutive tests ≥ 1+) for protein on urine dipstick. In the event of a positive test eligibility may be confirmed by a quantitative total urine protein measurement of < 500 mg/24 hrs
      - Persistently positive (2 out of 3 consecutive tests ≥ trace positive) for blood on urine dipstick. In the event of a positive test eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field
      - Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault < 50 mL/min (MDRD or CKD-EPI formulas can be used instead of Cockcroft-Gault for estimation of GFR in patients with low body weight after discussion with Sponsor Medical Monitor)

   c. Cardiac Troponin I > ULN at Qualification

   d. LDL-C > 130 mg/dL at Qualification

   e. Any other laboratory abnormalities which, in the opinion of the Investigator or the Sponsor, would make the patient unsuitable for inclusion

6. Uncontrolled hypertension (BP > 160/100 mm Hg)
7. History of thrombocytopenia (platelet count < 100,000/mm^3) or bleeding diathesis or coagulopathy or clinically-significant abnormality in coagulation parameters at Qualification
8. History of heart failure with NYHA greater than Class II

9. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1
10. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B
11. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated
12. Treatment with another investigational drug, biological agent, or device within 1 month of Qualification, or 5 half-lives of investigational agent, whichever is longer
13. Unwilling to comply with lifestyle requirements (Section 6.3)
14. Use of any of the following:
    a. Statins, omega-3 fatty acids (prescription and OTC), or fibrates unless on a stable dose for at least 3 months prior to Qualification and dose and regimen expected to remain constant during the treatment period. Patients taking OTC omega-3 fatty acids should make every effort to remain on the same brand throughout the study
    b. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to Qualification
    c. Systemic corticosteroids or anabolic steroids within 6 weeks prior to Qualification unless approved by the Sponsor Medical Monitor
    d. Atypical antipsychotic medications (e.g., olanzapine and clozapine) unless on a stable dose for at least 3 months prior to Qualification and dose and regimen expected to remain stable throughout the study
    e. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to Qualification and dose and regimen expected to remain constant during the treatment period
    f. Glybera gene therapy within 2 years prior to Qualification
    g. Oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, and apixaban) unless on a stable dose for at least 4 weeks prior to Qualification and regular clinical monitoring is performed
    h. Tamoxifen, estrogens or progestins unless on a stable dose for at least 4 months prior to Qualification and dose and regimen expected to remain constant during the treatment period
    i. Plasma apheresis within 4 weeks prior to Qualification or planned during the study
    j. Prior exposure to ISIS 304801
    k. Any other medication unless stable at least 4 weeks prior to Qualification (Occasional or intermittent use of over-the-counter medications will be allowed at Investigator's discretion)
15. Blood donation of 50 to 499 mL within 30 days of Qualification or of > 499 mL within 60 days of Qualification

16. Known hypersensitivity to any of the excipients of the Study Drug (ISIS 304801 or placebo)
17. Have any other conditions, including new or worsening of existing condition, which, in the opinion of the Investigator or the Sponsor would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the study

6. STUDY PROCEDURES

6.1 Study Schedule

All required study procedures are outlined in Appendices A, B, C, and D.

6.1.1 Qualification

Please refer to Section 4.1 and Appendix A.

6.1.2 Treatment Period

The patients, Investigators, study staff, and the Sponsor will remain blinded to lipid data through the last patient's Week 13 visit of the open-label study or until results from the database locks for the ISIS 304801-CS6 and ISIS 304801-CS16 index studies become available, whichever comes first.

During the treatment period, patients will report to the study center for clinic visits a minimum of 5 times during Weeks 1-52 (see Schedule of Procedures in Appendix A). Study Drug will be administered once weekly (Section 8.1). Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), AEs, concomitant medication/procedure information, lipid panel, blood viscosity, volanesorsen plasma concentrations, immunogenicity (IM) testing, platelet aggregation, liver/spleen MRI, ECGs, echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Adverse events at the injection site should be collected as adverse events. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period and all patients will complete a daily food diary for one week prior to their quarterly visit. All blood and urine samples should be collected prior to volanesorsen administration. Blood sampling at Weeks 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, and 51 may be conducted by a home healthcare nurse. Approval for study procedures to be conducted by a home healthcare nurse on other outpatient visit days will require prior approval by the Sponsor. Patients must be fasted prior to drawing all blood samples and samples drawn locally should also be sent to the central laboratory for analysis whenever possible. Dosing instructions and training will be provided to the patient where applicable.

All reasonable attempts should be made to ensure compliance with the visit schedule as outlined in Appendix A. However, in the event that a visit does not occur or is delayed, all subsequent visits should be calculated based on the time elapsed since Day 1 rather than from the date of the previous visit.

6.1.3 Pharmacokinetic (PK) Subgroup

A subgroup of patients will participate in an extended PK collection. Patients in this subgroup will have more frequent PK sampling over a 24-hour period following the first dose on Study Day 1 in order to evaluate the plasma PK parameters of volanesorsen. Patients in this subgroup will have an additional visit to the clinic, or by a home healthcare nurse, on Day 2 to collect a 24-hour post-dose blood draw after dosing on Day 1. The detailed PK sampling schedules are outlined in Appendix C.

Participation in the PK subgroup is optional for sites and patients, and consent may be withdrawn for the subgroup-specific procedures (e.g., multiple blood draws for PK) without being withdrawn from the study. If a patient withdraws consent from the subgroup procedures, he/she should remain on study and continue to follow all the non-subgroup assessments and procedures as outlined in Appendix A.

6.1.4 Post-Treatment Period

After completion of the Week 52 visit assessments, patients will enter the at least 26-week post-treatment evaluation period or will participate in an expanded access program pending approval by the IRBs/IEC, and the appropriate regulatory authorities. The 26-week period consists of at least 9 Study Center visits on Weeks 53, 54, 55, 56, 57, 58, 65, 71, and 78 (Weeks 53, 54, 55, 56, 57, 58, and 71 may be conducted by a home healthcare nurse), as outlined in the Schedule of Procedures in Appendix A.

6.2 Additional Study Assessments

6.2.1 Laboratory Assessments

Laboratory analyte samples will be collected throughout the study. A list of these analytes is contained in Appendix B.

Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1 week and the result must be reviewed by the Investigator and confirmed to be acceptable before dosing can continue. All platelet count results will be promptly reviewed by the Investigator to determine if the count has met a stopping rule, or the dose reduction rule of 100,000/mm^3, or the dose pause rule of 75,000/mm^3.

Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor.

6.2.2 Physical Exams and Vital Signs

Physical exams and vital signs will be performed as indicated in the Schedule of Procedures (Appendix A). Vital signs should include weight, blood pressure, pulse rate, respiratory rate and body temperature. Blood pressure and pulse rate will be recorded after the patient has been in a sitting position for at least 5 minutes. Semi-supine systolic and diastolic blood pressure should always be measured on the same arm (preferentially on the left arm). Height will be measured at the Day 1 visit.

6.2.2.1 Eruptive Xanthoma

At each visit, patients will be asked whether they have had any episodes of eruptive xanthoma since their last visit and the number/duration of the events will be recorded. Physical exams should also include skin examination for presence/resolution of eruptive xanthomas. If a patient experiences an episode of eruptive xanthoma during the study, photos of the area should be taken, if possible.

6.2.2.2 Lipemia Retinalis

If possible, lipemia retinalis will be assessed by fundus photography prior to administration of the first dose of Study Drug (for ISIS 304801-CS16 roll over patients) and repeated at Week 52. Images will be evaluated by an independent assessor, blinded to the patient's treatment assignment.

6.2.3 Echocardiography

Echocardiography for assessment of left and right ventricular function and mitral and aortic valve function will be conducted at Week 26 and Week 52 in all patients. For the purpose of assessment of treatment-emergent changes, all echocardiograms will be evaluated on an ongoing basis by an independent central reader. Results will be provided to the DSMB for their review.

6.2.4 ECG

The ECG will be recorded after the patient has been resting in a supine position for at least 5 minutes. ECGs will be performed in triplicate at Week 13, Week 26, Week 38, Week 52, Week 65, and Week 78.

6.2.5 MRI

MRI of the liver and spleen will be conducted at Week 52 for all patients for whom MRI is not contraindicated, e.g., patients having metal implants.

MRIs will be conducted using standardized procedures and settings. MRIs will be read by an independent central reader to assess liver fat and liver and spleen size**.**

6.2.6 Quality of Life Assessments

All patients will complete Quality of Life Questionnaires (EQ-5D and SF-36) at Week 1, Week 13, Week 26, Week 52, Week 65, and Week 78.

6.2.7 Disease Symptom Diary

All patients will complete a symptom questionnaire once a week starting at the beginning of the qualification period and continuing to the end of the post-treatment follow-up period.

6.2.8 Diet Monitoring

The diets of patients enrolled in the study will be monitored as follows:

1. All patients will be required to maintain a 7-day food diary prior to Week 1, Week 13, Week 26, Week 52, Week 65, and Week 78.

2. Patients will receive diet/alcohol counseling by qualified study personnel at clinic visits throughout the course of the study. Qualified study personnel will telephone the patient to provide diet/alcohol counseling for visits that are conducted by a clinical service.
3. In addition to the 7-day food diary and the diet /alcohol counseling during clinic visits, telephone calls from a dietitian or qualified study personnel to assess as to how each patient is maintaining their diet will be conducted randomly during the treatment and post treatment follow-up periods.

6.2.9 Family History

Family history of hypertriglyceridemia and pancreatitis will be collected for each patient.

6.2.10 Chart Review for Incidents of Acute Pancreatitis in Medical History (Group 2)

Patient records will be reviewed for incidents of acute pancreatitis occurring up to 5 years prior to screening and information relating to these events will be collected for independent adjudication.

6.3 Restriction on the Lifestyle of Patients

6.3.1 Contraception Requirements

All male patients and women of childbearing potential must refrain from sperm/egg donation and either be abstinent† or, if engaged in sexual relations of child-bearing potential, practice effective contraception from the time of signing the informed consent form until at least 13 weeks after their last dose of study treatment.

Male patients must also encourage their female partner to use effective contraception from the time of signing the informed consent until 13 weeks after the subject's last dose of study treatment.

For the purposes of this Study, women of childbearing potential are defined as any female who has experienced menarche, and who does not meet 1 of the following conditions:

- Postmenopausal: 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved
- 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Post hysterectomy

For the purposes of the study, effective contraception is defined as follows:

For male patients:

- Effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the use of condoms together with spermicidal foam/gel/film/ cream/suppository. Male patients must also encourage their female partner to use effective contraception from the time of signing the informed consent until 3 months after the patient's last dose of study treatment. Effective contraceptive for the female partner

includes: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or barrier methods (female condom*, diaphragm, sponge, cervical cap) together with spermicidal foam/gel/film/cream/suppository. Male patients with partners that are pregnant must use condoms to ensure that the fetus is not exposed to the Study Drug.

For female patients:

- Using 1 or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or any 2 barrier methods (a combination of male or female condom* with diaphragm, sponge, or cervical cap) together with spermicidal foam/gel/film/cream/suppository.

* Note: A female condom and a male condom should not be used together as friction between the two can result in either product failing.

† Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception

6.3.2 Other Requirements

All patients will be required to fast for at least 10 hours and preferably not more than 12 hours before visits requiring fasted blood sampling.

All patients will be encouraged to follow a diet comprising ≤ 20 g fat per day during the study.

Alcohol should not be consumed during the study.

All patients will be given an instruction card that must be presented to the treating physician if a suspected case of pancreatitis occurs. The card will explain that the patient is in a clinical trial and that serum lipase and/or amylase measures should be done in order to adjudicate the event, based on Atlanta Classification (Banks et al. 2013). If serum or amylase activity is less than 3 x upper limit of normal (ULN), imaging, preferably contrast-enhanced computed tomography, should be considered to confirm the diagnosis of acute pancreatitis per the Atlanta Criteria.

7. STUDY DRUG

7.1 Volanesorsen Description

Volanesorsen drug product (ISIS 304801) characteristics are listed in Table 1.

Volanesorsen (ISIS 304801) is contained in glass prefilled syringes (PFS). Volanesorsen and its storage and preparation instructions will be provided by the Sponsor or designee. Volanesorsen must be stored securely at 2 °C to 8 °C and be protected from light.

Table 1 Volanesorsen (ISIS 304801) Characteristics

Strength	200 mg/mL
Volume/Formulation	1.5 mL solution per PFS
Dose	300 mg once weekly
Route of Administration	SC

7.2 Packaging and Labeling

The Sponsor will provide the Investigator with packaged volanesorsen labeled (ISIS 304801) in accordance with specific country regulatory requirements.

7.3 Study Drug Accountability

The study staff is required to document the receipt, dispensing, and return/destruction of volanesorsen provided by the Sponsor. The Study Center must return all unused volanesorsen to the Sponsor or designee. All used syringes must be disposed of as per the site's hazardous waste destruction policy.

8. TREATMENT OF PATIENTS

8.1 Volanesorsen Administration

For each individual patient, volanesorsen will be administered subcutaneously as a single 1.5 mL 300 mg injection once weekly for Weeks 1-52. Patients entering this ISIS 304801-CS7 study on a reduced dose or dose frequency of Study Drug (volanesorsen), for safety or tolerability reasons in their index study (ISIS 304801-CS6 or ISIS 304801-CS16), will receive a reduced dose or dose frequency of volanesorsen for continued safety or tolerability as outlined in Sections 8.5 and 8.6. Patients entering this CS7 study having dose or dose frequency reduced in the CS16 index study after 13 weeks of treatment, as outlined in CS16 Amendment 4 Section 8.7, can receive the 300 mg once weekly dose of volanesorsen.

Patients should receive 1 dose per week, with weeks always defined relative to Study Day 1. For example if a patient receives the first dose on a Monday, subsequent doses should be given on Mondays, if possible. If a patient misses an injection, or if dosing on the usual day is not possible, the patient can reschedule the injection provided that 2 doses are administered at least 2 days apart.

Please refer to the Study Drug Manual provided by the Sponsor for more detailed instructions for volanesorsen preparation and administration.

8.2 Other Protocol-Required Drugs

There are no other protocol-required drugs.

8.3 Other Protocol-Required Treatment Procedures

There are no other protocol required treatment procedures for this study.

8.4 Treatment Precautions

There are no specific treatment precautions required for this study.

8.5 Safety Monitoring Rules

Please refer also to the 'Guidance for Investigator' section of the Investigator's Brochure.

For the purposes of safety monitoring baseline is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 (e.g., qualification assessments or assessments from the final visits of ISIS 304801-CS6 and ISIS 304801-CS16 index studies if used for qualification).

In addition to the standard monitoring of clinical safety parameters, the following guidelines are provided for the monitoring of selected parameters chosen based on preclinical and clinical observations.

Confirmation Guidance: At any time during the study (Treatment or Post-Treatment Periods), the initial clinical laboratory results meeting the safety monitoring or stopping criteria presented below **must be confirmed** by performing measurements (ideally in the same laboratory that performed the initial measurement) on new specimens. All new specimen collections should take place as soon as possible (ideally within 3 days of the initial collection). For stopping rules, if the initial laboratory result is observed during the Treatment Period, the results from the retest **must be available** prior to administering the next dose of volanesorsen.

In addition to the safety monitoring parameters listed below, the Sponsor may request confirmation of additional lab values.

Re-dosing Guidance: Patients with initial laboratory test values that reach a stopping rule must not be re-dosed until the re-test results are available. In general, patients who do not meet the stopping rules based upon retest may continue dosing. However, the Investigator and the Sponsor Medical Monitor (or appropriately qualified designee) should confer as to whether additional close monitoring of the patient is appropriate. Reduction in dose or dose frequency may also be initiated as noted in Section 8.7. If any of the stopping criteria described below (refer to Sections 8.6.1 to 8.6.3) are met, the patient will be dose paused or permanently discontinued (as described in the stopping criterion concerned) from further treatment with volanesorsen, and evaluated fully as outlined below and in consultation with the Sponsor Medical Monitor or appropriately qualified designee, and will be followed up in accordance with Section 8.8 of the protocol.

8.5.1 Safety Monitoring for Liver Chemistry Tests

The following rules are adapted from the draft guidance for industry, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," issued by the U.S. Department of Health and Human Services, Food and Drug Administration, July 2009. For a definition of Baseline please refer to guidance in Section 8.5 above.

In the event of an ALT or AST measurement that is > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) at any time during the study (Treatment or Post-Treatment Period), the initial measurement(s) should be confirmed as described above.

Additional confirmatory measurements should also be performed if ALT or AST levels increase to 5 x ULN.

Frequency of Repeat Measurements: Patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) should have their liver chemistry tests (ALT, AST, alkaline phosphatase (ALP), international normalized ratio (INR) and total bilirubin) retested at least once-weekly until ALT and AST levels become ≤ 1.2 x ULN or 1.2 x baseline value if the baseline value was > ULN.

Further Investigation into Liver Chemistry Elevations: For patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), the following evaluations should be performed:

1. Obtain a more detailed history of symptoms and prior and concurrent diseases
2. Obtain further history for concomitant drug use (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
3. Obtain a history for exposure to environmental chemical agents and travel
4. Serology for viral hepatitis (HAV IgM, HBsAg, HCV antibody, CMV IgM, and EBV antibody panel)
5. Serology for autoimmune hepatitis (e.g., antinuclear antibody [ANA])

Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic CT or MRI scans, may be performed at the discretion of the Investigator, in consultation with the Sponsor Medical Monitor. Repetition of the above evaluations should be considered if a patient's ALT and/or AST levels reach 5 x ULN.

8.5.2 Safety Monitoring for Platelet Count Results

Actions to be taken in the event of reduced platelet count are shown in Table 3 in Section 8.6.3.

Monitor every 1 week unless otherwise specified.

Study Drug administration is contingent on the availability of the immediately preceding test result. An interpretable platelet value must be available within 7 days prior to dosing. Only the study doctor or qualified designee can authorize continued Study Drug administration based on an acceptable platelet value. Patients should not administer a dose until they have been contacted by their study doctor or designee and told that it is acceptable to dose. Authorization to dose must be documented in the patient's medical records.

Due to the 1 to 2-year study duration it is anticipated that patients may undertake travel including vacations, which may impede weekly platelet monitoring. In some situations, it may be possible to arrange for local laboratory testing or use of the home healthcare service at their temporary location. The intent is to maintain weekly platelet monitoring and dosing where possible, as well as Investigator site contact with the study patients. However, if the above options are not possible, a temporary interruption of study treatment will be planned with a prompt blood draw

upon the patient's return which must be reported and reviewed by the Investigator prior to the patient resuming dosing.

The tests outlined in Table 2 should also be performed as soon as possible. Additional lab tests will be determined by the Sponsor Medical Monitor or designee in consultation with the Investigator.

Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor (See also Stopping Rules Section 8.6.3).

Table 2 Labs to Be Performed in the Event of a Platelet Count Less than the Lower Limit of Normal (x2) or < 100,000/mm^3 (x1)*

*In patients who have any 2 occurrences (consecutive or non-consecutive) of platelet count less than the lower limit of normal or who have any 1 occurrence of platelets < 100,000/mm^3. Labs only need to be performed once. Labs may be collected over multiple visits, if blood requirements are a concern, as per investigator discretion.

Note: The following labs may change as additional data is assessed, and sites will be updated regarding any changes.

To Be Performed at Local Lab
Peripheral smear (should be performed locally, fixed and sent to central lab for review)
Fibrinogen split products or D-dimer on fresh blood
To Be Performed at Central Lab
Citrated sample for platelets
Coagulation panel (PT/INR, aPTT)
CBC with reticulocytes
Folate (folic acid)
Vitamin B12
Fibrinogen
von Willebrand factor
Total globulins, total IgA, IgG and IgM
Complement: total C3, total C4, Bb, C5a
hsCRP
Helicobacter pylori (breath test)
Serology for:
HBV, HCV, HIV (if not done recently for screening)
Rubella
CMV
EBV
Parvo B19
Auto-antibody screen:
Antiphospholipid
Rheumatoid factor
Anti-dsDNA
Anti-thyroid
To Be Performed at Specialty Lab(s)
Antiplatelet antibodies and Anti-PF4 assay
Anti-ASO antibody

8.5.3 Safety Monitoring for Minor Bleeding Events

Minor bleeding events are those that do not fulfill the criteria for major bleeding or clinically-relevant, non-major bleeding events (which are defined in Section 8.6.3), for example excess bruising, petechiae, gingival bleeding on brushing teeth. If a minor bleeding event occurs, the Investigator must notify the Sponsor Medical Monitor and additional testing of coagulation parameters activated partial thromboplastin time (aPTT), prothrombin time (PT), INR and platelet count should be performed.

8.5.4 Safety Monitoring for Constitutional Symptoms

Patients will be instructed to promptly report any signs of symptoms of fever or constitutional symptoms that may arise during the study and the Investigator should closely evaluate all potential causes, including concomitant illness. Patients that experience persistent constitutional symptoms should be discussed with the Sponsor Medical Monitor or designee to determine whether additional monitoring or laboratory tests are required.

8.5.5 Safety Monitoring for LDL-C Elevations

Beginning at Week 13, laboratory alerts will be in place to notify the Investigator if a patient has a low-density lipoprotein-cholesterol (LDL-C) > 160 mg/dL (> 130 mg/dL for patients with T2DM) on 2 consecutive visits. If this occurs, LDL-C values for this patient will be unblinded for the remainder of the study and the Investigator will be encouraged to initiate/adjust treatment to lower LDL-C according to country-specific guidelines (e.g., initiate statin therapy or increase the statin dose for patients who are already on treatment).

8.5.6 Safety Monitoring for Insulin, Oral Antidiabetic Medication and Glucose

All patients on insulin will monitor their glucose levels with a glucometer as per standard practice guidelines and bring their glucometer or glucometer log printout to every clinic visit. In addition, patients who are not on insulin but use a glucometer should also bring their glucometer and/or glucometer log printout to every clinic visit.

- The Investigator or delegate will review the glucometer reading or printout at every clinic visit to evaluate if fasting pre-breakfast self-monitored plasma glucose values exceed threshold values as per the Safety Monitoring Rules for Hyperglycemia below.

All diabetic patients will note any changes in their insulin dose and /or oral antidiabetic therapy, as well as any hypoglycemic episode they may experience.

- The Investigator or delegate will ask patients at every clinic visit if they made changes in their insulin dose or oral antidiabetic therapy, and if they experienced a hypoglycemic episode.
    - Patients will be instructed on the monitoring and management of hypoglycemic episodes at each visit.
    - Documented symptomatic hypoglycemic episodes should be captured as adverse events in the adverse event CRF. Documented symptomatic hypoglycemia is defined as typical hypoglycemia symptoms accompanied by measured plasma glucose ≤ 70 mg/dL (≤ 3.9 mmol/L).

- Any changes in insulin dose or oral antidiabetic therapy should be captured into the Concomitant Medication CRF.

8.5.7 Safety Monitoring for Documented Severe Hypoglycemia

A **documented severe hypoglycemic event** is defined as one in which the patient requires assistance of another person to obtain treatment for the event and has a plasma glucose level ≤ 70 mg/dL (≤ 3.9 mmol/L). The rescue treatment of hypoglycemia may include IV glucose or buccal or intramuscular glucagon.

The definition of severe symptomatic hypoglycemia includes all episodes in which neurological impairment was severe enough to prevent self-treatment and which were thus thought to place patients at risk for injury to themselves or others. Note that "requires assistance" means that the patient could not help himself or herself. Someone being kind that assists spontaneously the patient when not necessary does not qualify as "requires assistance."

Severe hypoglycemia will be qualified as a SAE only if it fulfills SAE criteria.

If a patient presents with symptoms of hypoglycemia, the Investigator will need to take immediate action to confirm the patient's glucose level and treat the patient accordingly.

The experience of hypoglycemia may vary greatly from patient to patient. However, there are certain classical signs and symptoms, of which patients should be aware as a clue that their blood glucose may be low. Common symptoms include headache, heart pounding, confusion, disorientation, numbness or tingling, pale skin, shakiness or tremulousness, increased appetite, anxiousness or nervousness, lightheadedness or dizziness, sweating, and weakness. Coma could occur if blood sugar correction is not performed.

If patients suspect they might be having a hypoglycemia reaction, they should check their blood glucose using their meters as soon as possible, before treatment if possible, provided they feel it is safe to do so. If there is doubt about safety they should treat the event first, using some sugar, milk, or juice for example, then obtain and record a blood glucose value as soon as possible thereafter. The time and nature of treatment should be noted, and especially if any blood glucose result was before or after treatment. It would be helpful for the patient to note if a contributory factor (e.g., missed or reduced meals, unaccustomed physical activity) occurred earlier in the day of the event.

8.5.8 Safety Monitoring for Hyperglycemia

Upward dose titration and/or addition of any other anti-hyperglycemic agent(s) will not be allowed during the course of the study, unless specific threshold values are met at Week 13 or later and confirmed on subsequent testing (ideally within 1 week of the initial test).

HbA1c is monitored every 3 months throughout the study. In addition, patients on insulin should self-monitor their plasma glucose (SMPG) routinely on a glucometer as per practice guidelines. If a fasting pre-breakfast SMPG value exceeds the specific glycemic limit, the patient should check it again on the following 2 days. If all the fasting pre-breakfast values on 3 consecutive days exceed the specific limit, the patient should contact the Investigator and an unscheduled central laboratory FPG measurement and HbA1c should be performed.

The threshold values are defined as:

- FPG > 270 mg/dL (15.0 mmol/L)
- HbA1c > 9% (for patients with baseline HbA1c < 8% and HbA1c increase of more than 1% from baseline (for patients with baseline HbA1c ≥ 8 and < 9%)

In case of confirmed FPG/HbA1c above the threshold value, the Investigator should ensure that no reasonable explanation exists for insufficient glucose control and in particular that:

- Plasma glucose was actually measured in the fasting condition (i.e., after at least 10 hours fast)
- Absence of intercurrent disease which may jeopardize glycemic control. In case of an emergency (e.g., surgery, infection), the Investigator can take appropriate measures for glycemic control
- Compliance to treatment is appropriate
- Compliance to diet and lifestyle is appropriate

If any of the above can reasonably explain the insufficient glycemic control, the Investigator should consider the following:

- Investigation and treatment of intercurrent disease (to be reported in adverse event (AE)/concomitant medication parts of the e-CRF)
- Stress on the absolute need to be compliant to treatment
- Organize a specific interview with a Registered Dietician or other qualified nutrition professional and stress on the absolute need to be compliant to diet and lifestyle recommendations

A FPG/HbA1c follow-up assessment should be arranged after appropriate action has been taken. If none from the above-mentioned reasons can be found, or if appropriate action fails to decrease FPG/HbA1c under the threshold values, additional medication may be introduced at the Investigator's discretion and according to local guidelines after discussion with the Sponsor Medical Monitor.

8.5.9 Acute Pancreatitis

If a patient has an episode of acute pancreatitis, dosing with Study Drug should be suspended temporarily until the patient is clinically stable. The suitability of the patient for continued dosing and the need for any modification to treatment schedule (refer to Section 8.7) will be determined by the Investigator in consultation with the Study Medical Monitor.

8.6 Stopping Rules

For the purposes of stopping rules baseline is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1.

8.6.1 Stopping Rules for Liver Chemistry Elevations

In the event of laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor,** dosing of a patient with volanesorsen will be stopped permanently; values that are not confirmed due to failure to retest or missing lab values will be presumed confirmed:

1. ALT or AST > 8 x ULN, which is confirmed
2. ALT or AST > 5 x ULN, which is confirmed and persists for ≥ 2 weeks
3. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed **and** total bilirubin > 2 x ULN or INR > 1.5
4. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed, and the new appearance (i.e., onset coincides with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> ULN) felt by the Investigator to be potentially related to hepatic inflammation

8.6.2 Stopping Rules for Renal Function Test Results

In the event of a persistent elevation that is observed over 2 consecutive weeks, for any of the 3 criteria below, dosing of a patient with volanesorsen may be stopped temporarily:

1. Serum creatinine increase that fulfill all of the following criteria: ≥ 0.3 mg/dL (26.5 µmol/L) and ≥ 40% above baseline creatinine values and > ULN
2. Proteinuria, dipstick 2 + (confirmed by dipstick retest and then further confirmed by a quantitative total urine protein measurement of > 1.0 g/24 hour)
3. Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault ≤ 40 mL/min that is confirmed by a 24-hour urine collection

The possible dosing re-initiation or follow-up schedule for any events meeting either of these criteria will be determined by the Investigator **in consultation with** the Sponsor Medical Monitor or designee.

8.6.3 Stopping Rules for Platelet Count Results

Actions to be taken in the event of a low platelet count are summarized in Table 3 below.

In the event of a platelet count less than 75,000/mm^3 that is associated with major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with volanesorsen will be stopped permanently. The follow-up schedule for any events meeting this stopping criterion will be determined by the Investigator in consultation with the Sponsor Medical Monitor.

In the event of any platelet count less than 50,000/mm^3, or a rate of decline ≥ 50% between two consecutive assessments, irrespective of the platelet level, or a platelet count less than 75,000/mm^3 that occurs while the patient is on dosing at 300 mg every 2 weeks, then dosing of a patient with volanesorsen will be stopped permanently. Platelet count will be monitored as outlined in Table 3.

Administration of steroids is recommended for patients whose platelet count is less than 50,000/mm^3. Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (**note:** may require continuation with oral steroids after methylprednisolone). In order to reduce the unlikely but potential increased risk of pancreatitis during the period of corticosteroid therapy, triglyceride levels will be monitored weekly, and AE monitoring will continue, during corticosteroid treatment and the laboratory alert will be changed from an increase of 2,000 to 500 mg/dL during that period.

In the event of a platelet count less than 75,000/mm^3, and in the absence of major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with volanesorsen should be suspended temporarily until the platelet count has recovered to> 100,000/mm^3. If dosing is continued it should be at a reduced dose frequency of 300 mg every 2 weeks (refer to Section 8.7). The suitability of the patient for continued dosing will be determined by the Investigator in consultation with the Study Medical Monitor and will be based on factors such as the original rate of decline in the patient's platelet count, whether any bleeding events were experienced by the patient, and the speed of recovery of platelet count upon holding of dosing.

If after the first dosing rechallenge the platelet count again falls below 75,000/mm^3, then dosing of the patient with Study Drug will be stopped permanently.

Definition of Major Bleeding Events (Schulman et al. 2005):

- Fatal bleeding, and/or
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarterial or pericardial, or intramuscular with compartment syndrome, and/or
- Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more within 24 hours, or leading to transfusion of 2 or more units of whole or red cells

Definition of Clinically-Relevant, Non-Major Bleeding Events (Schulman et al. 2005):

1. Multiple-source bleeding
2. Spontaneous hematoma > 25 cm^2
3. Excessive wound hematoma (not injection site related)
4. Macroscopic hematuria (spontaneous or lasting > 24 hours if associated with an intervention)
5. Spontaneous rectal bleeding; epitasis, gingival bleeding, hemoptysis, hematemesis
6. Bleeding after venipuncture for > 5 minutes

Table 3 Actions in Patients with Low Platelet Count

Platelet Count on Rx	Drug Dose	Monitoring
	Study Drug administration is contingent on the availability of the immediately preceding test result. An interpretable platelet value must be available within 7 days prior to dosing. Only the study doctor or qualified designee can authorize continued Study Drug administration based on an acceptable platelet value. Patients should not administer a dose until they have been contacted by their study doctor or designee and told that it is acceptable to dose. Authorization to dose must be documented in the patient's medical records.	Monitor every 1 week unless otherwise specified Obtain additional lab tests (Table 2) if 2 occurrences consecutive or non-consecutive of platelet count 140K - > 100K/mm^3 or 1 occurrence of platelet count ≤ 100K/mm^3. Labs only need to be performed once. Labs may be collected over multiple visits, if blood requirements are a concern, as per Investigator discretion.
> 100K/mm^3	Weekly 300 mg Study Drug administration	
100K/mm^3 - >75K/mm^3	Permanently reduce dose frequency to 300 mg every 2 weeks	
75K/mm^3 - >50K/mm^3	• If occurs while on dose of 300 mg every 2 weeks then permanently discontinue Study Drug, otherwise dose pause. • When platelet count returns to > 100K/mm^3 restart dosing at dose frequency of 300 mg every 2 weeks **only if approved by Sponsor Medical Monitor**	• Monitor every 2-3 days until 2 successive values are > 75K/mm^3 then monitor every 1 week • Consider discontinuation of antiplatelet agents/NSAIDS/ anticoagulant medication
< 50K/mm^3 or a rate of decline ≥ 50% between two consecutive assessments, irrespective of the platelet level	Permanently discontinue Study Drug	• Monitor daily until 2 successive values show improvement then monitor every 2-3 days until 2 successive values are > 75K/mm^3 then monitor every 1 week • Patient should be evaluated by a hematologist to provide diagnostic and therapeutic management • Steroids recommended if platelet count is < 50K/mm^3*. It is strongly recommended that, unless the patient has a medical contraindication to receiving glucocorticoids, the patient receives glucocorticoid therapy to reverse the platelet decline. • Monitor triglyceride levels weekly and continue AE monitoring during steroid therapy • Discontinue antiplatelet agents/ NSAIDS/ anticoagulant medication while platelet count is< 50K/mm^3 if possible

Table 3 Actions in Patients with Low Platelet Count *Continued*

Legend:

* Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (**note**: may require continuation with oral steroids after methyl prednisolone). In order to reduce the unlikely but potential increased risk of pancreatitis during the period of corticosteroid therapy, triglyceride levels will be monitored weekly, and AE monitoring will continue, during corticosteroid treatment and the laboratory alert will be changed from an increase of 2,000 to 500 mg/dL during that period.

8.7 Adjustment of Dose Frequency

Dose adjustments for platelet count reduction must be made in accordance with Section 8.6.3 and Table 3 (above).

Other dose adjustments, including dose interruptions, and/or decreasing the dose or dose frequency will be allowed for safety and tolerability. Any proposed adjustment to treatment schedule must be discussed with, and approved by, the Study Medical Monitor prior to initiation. Up to 2 adjustments in the treatment schedule may be allowed.

Patients may be dose paused in response to AEs after consultation with Study Medical Monitor.

8.8 Discontinuation of Study Treatment

A patient must permanently discontinue study treatment for any of the following:

- The patient becomes pregnant. Report the pregnancy according to instructions in Section 9.5.4
- The patient withdraws consent
- The patient experiences an AE that necessitates permanent discontinuation of study treatment
- The patient develops laboratory test abnormalities that meet any of the stopping rules listed in Section 8.6

The reason for discontinuation of study treatment must be recorded in the CRF and source documentation.

8.8.1 Follow-up Visits for Early Termination from Treatment Period

Any patient who discontinues early from the Treatment Period should be followed as per the platelet monitoring rules shown in Table 3 in Section 8.6.3 for the first 6 weeks after discontinuing Study Drug. Following this period, if the platelet count is stable (at least 3 consecutive values that are stable as determined by the Sponsor Medical Monitor and $> 100{,}000/mm^3$), the next platelet count should be taken within at least 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug. Patients should also be strongly encouraged to attend applicable landmark visits at Weeks 12, 13, 25, 26, and 50, 52 (calculated based on the time elapsed since Day 1) to collect fasting lipid panels and conduct safety assessments in accordance with the Schedule of Procedures in Appendix A. Any patient

who discontinues treatment after Week 44 should also be strongly encouraged to attend a final follow-up visit (Week 78 visit assessments) approximately 26 weeks after their last dose of Study Drug, in addition to the applicable landmark visits.

If the patient declines or is unable to participate in the above, an early termination (ET) visit (Week 52 visit assessments) should be performed at the time of withdrawal, at a minimum, and ideally within 2 weeks from the last dose of Study Drug.

8.8.2 Follow-up Visits for Early Termination from Post-Treatment Follow-up Period

The patient who requests to withdraw from the study during the Post-Treatment Follow-up Period should be encouraged to follow the platelet monitoring rules shown in Table 3 in Section 8.6.3 for the first 6 weeks after discontinuing Study Drug. Following this period, if the platelet count is stable (at least 3 consecutive values that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3), the next platelet count should be taken within at least 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug. Patients should also be encouraged to undergo a final follow-up visit (Week 78, see Appendix A) prior to leaving the study.

If a patient withdraws due to an AE at any time during the study, the Investigator should arrange for the patient to have appropriate follow-up until the AE has resolved or stabilized.

8.9 Withdrawal of Patients from the Study

Patients must be withdrawn from the study for any of the following:

- Withdrawal of consent
- The patient is unwilling or unable to comply with the protocol

Other reasons for withdrawal of patients from the study might include:

- At the discretion of the Investigator for medical reasons
- At the discretion of the Investigator or Sponsor for noncompliance
- Significant protocol deviation

All efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information, including the reason for withdrawal from study, must be recorded in the CRF.

Any patient who withdraws consent to participate in the study will be removed from further treatment and study observation immediately upon the date of request. These patients should be encouraged to complete the ET study procedures and observations at the time of withdrawal (see Section 8.8 and Appendix A).

For patients withdrawn for reasons other than withdrawal of consent every effort should be made to complete the early termination study procedures and observations at the time of withdrawal (see Section 8.8 and Appendix A).

8.10 Concomitant Therapy and Procedures

The use of concomitant therapies or procedures defined below must be recorded on the patient's CRF. AEs related to administration of these therapies or procedures must also be documented on the appropriate CRF.

8.10.1 Concomitant Therapy

A concomitant therapy is any non-protocol specified drug or substance (including over-the-counter medications, herbal medications and vitamin supplements) administered between signing informed consent and completion of the post-treatment follow-up period. All concomitant medications/treatments and significant non-drug therapies (including supplements and assistive devices) received by a patient, including changes in the patient's current medications, must be recorded in the patient's source documents and CRF. Patients taking over the counter (OTC) omega-3 fatty acids should make every effort to remain on the same brand throughout the study.

Allowed Concomitant Therapy

Any medications deemed necessary by the Investigator are allowed except those listed in the disallowed concomitant therapy.

Disallowed Concomitant Therapy

No lipid lowering therapies (e.g., fibrates, niacin, fish oil or other products containing omega-3 fatty acids [including OTC preparations]), -glucagon-like peptide-1 (GLP-1) agonists, Glybera, or systemic corticosteroids may be started or adjusted after baseline Qualification. Doses of existing oral anti-diabetic medication, oral contraceptives, hormone replacement therapy, anticoagulants, or drugs or dietary supplements with potential lipid-altering effects should not be adjusted. Study patients are prohibited from receiving other experimental agents during the study. This includes marketed agents at experimental dosages that are being tested for the treatment of hypertriglyceridemia.

Patients should consult with the Site Investigator or designee prior to initiating any new medication, including non-prescription or herbal compounds or any other non-drug therapy.

8.10.2 Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between signing of informed consent and Week 78 visit.

Disallowed Concomitant Procedure

Plasma apheresis is not allowed during the study.

8.11 Treatment Compliance

Compliance with treatment dosing is to be monitored and recorded by Study Center staff. The Study Center staff is required to document the receipt, dispensing, and return/destruction of volanesorsen. Patients that are self-administering volanesorsen at home must record treatment in a dosing diary that will be reviewed periodically by Study Center staff and the Clinical Monitor.

9. SERIOUS AND NON-SERIOUS ADVERSE EVENT REPORTING

9.1 Sponsor Review of Safety Information

Safety information will be collected, reviewed, and evaluated by the Sponsor in accordance with the Safety Management Plan throughout the conduct of the clinical trial.

9.2 Regulatory Requirements

The Sponsor is responsible for regulatory submissions and reporting to the Investigators of serious adverse events (SAEs) including suspected unexpected serious adverse reactions (SUSARs) per the International Conference on Harmonization (ICH) guidelines E2A and ICH E6. Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines.

Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) will be notified of any SAE according to applicable regulations. The Independent DSMB will be notified of any SAE as specified in the DSMB charter.

In addition to the Investigator's assessment of relatedness, the Sponsor or designee will evaluate the available information and perform an independent assessment of relatedness. While the Sponsor may upgrade an Investigator's decision it is not permissible to downgrade the Investigator's opinion for the purposes of determining whether the SAE meets the definition of a SUSAR.

The following table identifies the SAEs that the Sponsor or designee will not report on an individual basis in an expedited manner because they are anticipated to occur in the study population independent of volanesorsen exposure. The Investigator still has the responsibility to report all SAEs to the Sponsor as described in Sections 9.4.1 to 9.4.3.5.

Table 4 Expected Event for the Protocol Defined Population by Preferred Term and the Expected Incidence

Preferred Term	Expected Incidence in the Protocol Defined Population (Gaudet et al. 2010 and 2013)
Pancreatitis associated events including the PTs of hereditary pancreatitis, pancreatitis, pancreatitis acute, pancreatitis chronic, pancreatitis necrotizing, pancreatitis relapsing	0.2-0.35 events per patient-year

Fatal pancreatitis associated events will be considered as unexpected and are reportable. The Sponsor and DSMB will monitor non-fatal pancreatitis associated SAEs using the incidence rate of the event compared to the rate expected in a non-volanesorsen exposed population. If the aggregate analysis indicates that an event is occurring significantly more frequently or at a greater severity than expected, then the event will be reported.

SAEs not specified in the table will be evaluated on case by case basis to determine whether there is a reasonable possibility that the drug caused the event. If the event is considered by the Sponsor or designee to meet the definition of a SUSAR the event will be reported.

9.3 Definitions

9.3.1 Adverse Event

An adverse event is any unfavorable and unintended sign (including a clinically-significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the study or use of investigational drug product, whether or not the AE is considered related to the investigational drug product.

9.3.2 Adverse Reaction and Suspected Adverse Reaction

An adverse reaction is any adverse event caused by volanesorsen.

A suspected adverse reaction is any adverse event for which there is a reasonable possibility that volanesorsen drug caused the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

9.3.3 Serious Adverse Event (SAE)

A serious adverse event is any adverse event that in the view of either the Investigator or Sponsor, meets any of the following criteria:

- Results in death
- Is life threatening: that is, poses an immediate risk of death at the time of the event

An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Hospitalization is defined as an admission of greater than 24 hours to a medical facility and does not always qualify as an AE
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly or birth defect in the offspring of the patient (whether the patient is male or female)
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

9.4 Monitoring and Recording Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the study (i.e., before informed consent) should be recorded as Medical History and not recorded as AEs unless the pre-existing condition worsened. The Investigator should always group signs and symptoms into a single term that constitutes a **single unifying diagnosis** if possible.

9.4.1 Serious Adverse Events

In the interest of patient safety, and in order to fulfill regulatory requirements**,** all SAEs (regardless of their relationship to volanesorsen) should be reported to the Sponsor or designee within 24 hours of the Study Center's first knowledge of the event. The collection of SAEs will begin after the patient signs the informed consent form and stop at the end of the patient's follow-up period which is defined as the Week 78 visit. When the Investigator is reporting by telephone, it is important to speak to someone in person versus leaving a message. An Initial Serious Adverse Event Form should be completed and a copy should be faxed to the Sponsor or designee.

Detailed information should be actively sought and included on Follow-Up Serious Adverse Event Forms as soon as additional information becomes available. All SAEs will be followed until resolution. SAEs that remain ongoing past the patient's last protocol-specified follow-up visit will be evaluated by the Investigator and Sponsor. If the Investigator and Sponsor agree the patient's condition is unlikely to resolve, the Investigator and Sponsor will determine the follow-up requirement.

9.4.2 Non-Serious Adverse Events

The recording of non-serious AEs will begin after the patient signs the informed consent form and will stop at the end of the patient's follow-up period, which is defined as the Week 78 visit. The Investigator will monitor each patient closely and record all observed or volunteered AEs on the Adverse Event Case Report Form.

9.4.3 Evaluation of Adverse Events (Serious and Non-Serious)

The Investigator's opinion of the following should be documented on the Adverse Event Case Report Form:

9.4.3.1 Relationship to the Study Drug

The event's relationship to volanesorsen is characterized by 1 of the following:

- **Related:** There is clear evidence that the event is related to the use of volanesorsen, e.g., confirmation by positive rechallenge test
- **Possible:** The event cannot be explained by the patient's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and volanesorsen administration

- **Unlikely/Remote:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to volanesorsen administration and/or exposure suggests that a causal relationship is unlikely (For reporting purposes, Unlikely/Remote will be grouped together with Not Related)
- **Not Related:** The event can be readily explained by the patient's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and volanesorsen

9.4.3.2 Severity

The severity of AEs and SAEs will be graded based on criteria from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010 (refer to Appendix D). Any AE not listed in Appendix D will be graded as follows:

- **Mild:** The event is easily tolerated by the patient and does not affect the patient's usual daily activities
- **Moderate:** The event causes the patient more discomfort and interrupts the patient's usual daily activities
- **Severe:** The event is incapacitating and causes considerable interference with the patient's usual daily activities

If the event is an SAE, then all applicable seriousness criteria must be indicated (criteria listed in Section 9.3.3).

9.4.3.3 Action Taken with Volanesorsen

Action taken with volanesorsen due to the event is characterized by 1 of the following:

- **None:** No changes were made to volanesorsen administration and dose
- **Permanently Discontinued:** Volanesorsen was discontinued and not restarted
- **Temporarily Interrupted, restarted – same dose:** Dosing was temporarily interrupted or delayed due to the AE and restarted at the same dose
- **Reduced schedule:** Dosing frequency was reduced

9.4.3.4 Treatment Given for Adverse Event

Any treatment (e.g., medications or procedures) given for the AE should be recorded on the Adverse Event Case Report Form (treatment should also be recorded on the concomitant treatment or ancillary procedures CRF as appropriate).

9.4.3.5 Outcome of the Adverse Event

If the event is a non-serious AE then the event's outcome is characterized by 1 of the following:

- **AE Persists:** Patient terminates from the trial and the AE continues
- **Recovered:** Patient recovered completely from the AE

- **Became Serious:** The event became serious (the date that the event became serious should be recorded as the Resolution Date of that AE and the Onset Date of the corresponding SAE)
- **Change in Severity** (if applicable): AE severity changed

If the event is a SAE then the event's outcome is characterized by 1 of the following:

- **Ongoing:** SAE continuing
- **Persists (as non-serious AE):** Patient has not fully recovered but the event no longer meets serious criteria and should be captured as an AE on the non-serious AE eCRF (the SAE resolution date should be entered as the date of onset of that AE)
- **Recovered:** Patient recovered completely from the SAE (the date of recovery should be entered as the SAE resolution date)
- **Fatal:** Patient died (the date of death should be entered as the SAE resolution date)

9.4.4 Adjudication Committees

All SAEs that occur during the study that are consistent with a major acute cardiovascular event (MACE) will be adjudicated by a blinded, independent committee as outlined in the MACE Adjudication Charter.

All AEs and SAEs that occur during the study that are consistent with an event of acute pancreatitis will be adjudicated by a blinded, independent committee according to the Atlanta classification of acute pancreatitis (Banks et al. 2013) and as outlined in the Pancreatitis Adjudication Charter. In addition, data for prior episodes of acute pancreatitis or suspected pancreatitis will be collected by review of each patient's medical chart and these events will also be adjudicated.

9.5 Procedures for Handling Special Situations

9.5.1 Abnormalities of Laboratory Tests

Clinically-significant abnormal laboratory test results may, in the opinion of the Investigator, constitute or be associated with an AE. Examples of these include abnormal laboratory results that are associated with symptoms, or require treatment, e.g., bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac arrhythmias due to hyperkalemia. Whenever possible, the underlying diagnosis should be listed in preference to abnormal laboratory values as AEs. Clinically-significant abnormalities will be monitored by the Investigator until the parameter returns to its baseline value or until agreement is reached between the Investigator and Sponsor Medical Monitor. Laboratory abnormalities deemed not clinically-significant (NCS) by the Investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator should not be deemed NCS on the laboratory sheet.

The Investigator is responsible for reviewing and signing all laboratory reports. The signed clinical laboratory reports will serve as source documents and should include the Investigator's assessment of clinical significance of out of range/abnormal laboratory values.

9.5.2 Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the patient is hospitalized; the Study Center must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the patient's consent to participate in the study
- The condition that required the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the patient's consent to participate in the study and the timing of the procedure or treatment
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission

9.5.3 Dosing Errors

Volanesorsen dosing errors should be documented as Protocol Deviations. A brief description should be provided in the deviation, including whether the patient was symptomatic (list symptoms) or asymptomatic, and the event accidental or intentional.

Dosing details should be captured on the Dosing Case Report Form. If the patient takes a dose of volanesorsen that exceeds protocol specifications and the patient is symptomatic, then the symptom(s) should be documented as an AE and be reported per Section 9.4.

Should an overdose occur, the Investigator or designee should refer to the Guidance to Investigator's section of the Investigator's Brochure and contact the Sponsor or designee within 24 hours.

9.5.4 Contraception and Pregnancy

Male patients and female patients of childbearing potential must continue to use appropriate contraception with their partners, or refrain from sexual activity, as described in Section 6.3.1.

If a patient becomes pregnant or a pregnancy is suspected, or if a male patient makes or believes that he has made someone pregnant during the study, then the Study Center staff must be informed immediately. An Initial Pregnancy Form should be submitted to the Sponsor or designee **within 24 hours** of first learning of the occurrence of pregnancy. Follow-up information including delivery or termination is reported on Follow-up Pregnancy Forms and reported within 24 hours.

Payment for all aspects of obstetrical care, child or related care will be the patient's responsibility.

Female patients: If a suspected pregnancy occurs while on the study (including follow-up), a pregnancy test will be performed. The patient with a confirmed pregnancy will be immediately withdrawn from treatment with volanesorsen. However, the patient will be encouraged to complete the post-treatment follow-up portion of the study to the extent that study procedures do not interfere with the pregnancy. Regardless of continued study participation, the study

physician will assist the patient in getting obstetrical care and the progress of the pregnancy will be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the Study Center and Sponsor may require access to the mother and infant's medical records for an additional 8 weeks after birth.

Male patients: The progress of the pregnancy in a male patient's partner should be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, **the Study Center and Sponsor may request access to the mother and infant's medical records for an additional 8 weeks after birth**. Follow-up will be performed to the extent permitted by applicable regulations and privacy considerations.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints

For fasting lipid measurements, the values at Month 3 analysis time point are defined as the average of Week 12 (Day 78) and Week 13 (Day 85) fasting assessments, the values of Month 6 analysis time point is at the end of Month 6 are defined as the average of Week 25 (Day 169) and Week 26 (Day 176) fasting assessments, and the values at the Month 12 analysis time point are defined as the average of Week 50 (Day 344) and Week 52 (Day 358) fasting assessments.

10.1.1 Efficacy Endpoints

- Percent change and absolute change from baseline in fasting TG
- Frequency and severity of patient reported abdominal pain during the treatment period
- Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-HDL-C, apoB, HDL-C, apolipoprotein A-1 (apoA-1), VLDL-C, and LDL-C
- Percent change from baseline in fasting total apolipoprotein C-III
- Change in blood viscosity (may be evaluated)
- Quality of Life questionnaires (EQ-5D, SF-36)
- Adjudicated acute pancreatitis event rate
- Other symptoms: eruptive xanthoma, lipemia retinalis

10.1.2 Safety Endpoints

- Adverse events including adjudicated events of pancreatitis and MACE
- Vital signs and weight
- Physical examinations
- Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis)
- Echocardiography

- Electrocardiograms (ECGs)
- Use of concomitant medications
- MRIs
- Platelet aggregation (may be evaluated)

10.2 Sample Size

No sample size calculations were performed as this is an open-label study.

10.3 Populations

Full Analysis Set (FAS): All patients who are enrolled and received at least 1 dose of active Study Drug and have a baseline TG assessment. The FAS represents the practically-feasible intent-to-treat (ITT) population as delineated in ICH Guideline E9.

Per Protocol Set (PPS): Subset of the FAS who received 9 of first 13 scheduled doses of volanesorsen and with no significant protocol deviations that would be expected to affect efficacy and PD assessments. The detailed criteria will be specified and finalized prior to the final database lock.

Safety Set: All patients who are enrolled and receive at least 1 dose of volanesorsen.

PK Population: All patients who are enrolled, receive at least 1 dose of volanesorsen, and have at least 1 post first dose PK sample collected, analyzed, and reported.

10.4 Definition of Baseline

Definitions of baseline are given below for the purposes of the final analysis.

For fasting lipid measurements, 2 baselines are defined for each patient in Groups 1 and 2: Group 1 (ISIS 304801-CS6) or Group 2 (ISIS 304801-CS16) index study baseline and the baseline in this open-label study, which is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 (e.g., qualification assessments or assessments from final visit of the ISIS 304801-CS6 or ISIS 304801-CS16 index studies if used for qualification).

For other measurements, baseline for patients on active treatment in the ISIS 304801-CS6 or ISIS 304801-CS16 index study will be the ISIS 304801-CS6 or ISIS 304801-CS16 index study baseline. For patients on placebo in the ISIS 304801-CS6 or ISIS 304801-CS16 index study, baseline will be the last non-missing assessment prior to the first dose of Study Drug. Details will be provided in the SAP.

10.5 Interim Analysis

An interim analysis may be conducted after the last patient's Week 13 visit of the open-label study or after the database of the ISIS 304801-CS6 and ISIS 304801-CS16 index studies are locked and unblinded. Both safety and efficacy information from this open-label study may be summarized during this interim analysis. Efficacy analyses will be detailed in the SAP.

10.6 Planned Methods of Analysis

All eCRF data, lab data transfers, as well as any outcomes derived from the data, will be provided in the patient data listings. Patient data listings will be presented for all patients enrolled into the study. Descriptive summary statistics including n, mean, median, standard deviation, standard error, interquartile range (25th percentile, 75th percentile), and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data by treatment group of the index studies for patients on active Study Drug in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies, and pooled treatment naïve group which includes patients on placebo in index studies. Where appropriate, p-values will be reported. All statistical tests will be conducted using 2-sided tests with 5% Type I error rates unless otherwise stated.

TG related endpoints will be assessed in the FAS and PPS, and all other efficacy endpoints will be assessed in the FAS. All safety assessments will be performed on the Safety Set. PK endpoints will be assessed in the PK Set as applicable.

10.6.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics by treatment group and overall. The patient disposition will be summarized by treatment group and overall. All patients enrolled will be included in a summary of patient disposition.

10.6.2 Safety Analysis

Treatment duration and amount of Study Drug received will be summarized by treatment group and overall.

Patient incidence rates of AEs will be tabulated by MedDRA system organ class, MedDRA preferred term, and treatment group of the index studies. Narratives of treatment-emergent deaths, serious and significant AEs, including early withdrawals due to AEs, will also be provided.

All treatment-emergent AEs, all treatment-emergent AEs potentially related to Study Drug, all treatment-emergent serious AEs, and all treatment-emergent serious AEs potentially related to Study Drug will be summarized.

Injection Site Reactions (ISRs) will be summarized by treatment group, MedDRA preferred term and severity.

Independently adjudicated events of MACE and pancreatitis will be summarized by treatment group.

Laboratory tests to ensure patient safety including chemistry panel, complete blood count (CBC) with differential, coagulation panel, IM, complement etc., will be summarized by study visits by treatment group.

These safety variables will also be presented as change and percent change from baseline over time after Study Drug administration, as appropriate.

Vital signs, weight, ECG measures, echocardiography assessments, and MRI assessments will be tabulated by treatment group.

10.6.3 Efficacy Analysis

Percent change and change from baseline to Month 3, Month 6, and Month 12 in fasting TG will be summarized by treatment group. Response rate of patients with fasting plasma TG < 750 mg/dL or achieving fasting TG ≥ 40% reduction from baseline at Month 3, Month 6, and Month 12 will be summarized. Response analysis will also be conducted using a range of fasting plasma TG thresholds for determination of responder status.

Percent change and change from baseline to Month 3, Month 6, and Month 12 will also be summarized by treatment group for other fasting lipid measures including non-HDL-C, apoB, HDL-C, apoA-1, VLDL-C, and LDL-C, total cholesterol, and fasting total apoC-III.

The incremental effects of volanesorsen on lipid measures will be explored and the association between changes in lipid parameters and total amount of drug received will be examined, as appropriate.

Frequency and severity of patient reported abdominal pain, adjudicated acute pancreatitis event rate, quality of life assessments, and comparison of other symptoms including eruptive xanthomas and lipemia retinalis will be summarized by treatment group.

Additional details of the analyses to be conducted will be provided in the SAP.

10.6.4 Pharmacokinetic and Immunogenicity Analysis

10.6.4.1 Pharmacokinetic Analysis

For all patients, pre-dose and post-treatment volanesorsen plasma concentrations will be summarized using descriptive statistics by treatment group and IM status.

For patients in the PK subgroup only, non-compartmental PK analysis of volanesorsen will be carried out on each individual patient data set using data collected in the open-label study from the intensive PK subgroup, following a single-dose (i.e., single-dose PK) or multiple doses (i.e., steady-state PK), depending on their earlier treatment in the index studies (Group 1 and 2 patients). On Week 1 Day 1 of the open-label study, patients who received placebo in the index study will receive the first treatment of volanesorsen (single-dose PK), while patients who received volanesorsen in the index studies had been on volanesorsen treatment for 12 months (ISIS 304801-CS6) or 6 months (ISIS 304801-CS16), thus the PK data collected from these patients reflect steady-state PK. The maximum observed drug concentration (C_{max}) and the time taken to reach C_{max} (T_{max}) will be obtained directly from the concentration-time data. Area under the plasma concentration-time curve from time zero to 24 hours (AUC_{0-24h}) will be calculated using the linear trapezoidal rule. Apparent systemic (plasma) clearance after SC administration (CL_{0-24h} /F) will be calculated from CL_{0-24h} /F = Actual Dose/AUC_{0-24h}. Mean residence time (MRT) from time zero to 24 hours after the SC administration will be calculated from the equation, $MRT_{0-24h} = AUMC_{0-24h}/AUC_{0-24h}$, where $AUMC_{0-24h}$ is the area under the moment plasma concentration-time curve from time zero to 24 hours after the SC administration. Other PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist.

Plasma PK parameters will be summarized using descriptive statistics by treatment group and IM status. Additional details regarding the PK analysis will be described in the SAP.

Population PK, PK/PD, and covariate analysis may be performed if deemed appropriate, and results will be reported separately.

10.6.4.2 Immunogenicity Analysis

Immunogenicity (IM) results (screen positive/negative, confirmed positive/negative or not evaluable, and when applicable, titer of anti-volanesorsen antibodies) before, during, and after treatment with Study Drug (volanesorsen) (i.e., sample [anti-drug antibody] ADA status) will be listed by their prior treatment in study ISIS 304801-CS6 or ISIS 304801-CS16 (Groups 1 and 2) and study day. Subject ADA status (positive/negative or not evaluable) for all evaluable patients, along with the study day associated with the first positive IM status emerged (T_{first}, i.e., onset of ADA development), the last positive IM status observed (T_{last}), the last ADA sample collection day, and subject - peak titer if applicable, will be listed by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16 (Groups 1 and 2) and study day. Subjects with positive anti-volanesorsen antibody status may be further classified (when applicable) as being either 'persistent', 'transient', or 'not determinable', if deemed appropriate.

Additionally, the sample and subject IM incidence (number) and incidence rate (percent) will be summarized as the total number and percent of evaluated subjects with antibody negative, positive, and unknown status by treatment group. Furthermore, onset and titer of the ADA response, if applicable, will be summarized as median, quartiles (25% and 75%), and range.

Additional details regarding the IM data analysis will be described in the SAP.

Potential relationships between immunogenicity results (e.g., IM status) and selected efficacy (e.g., %change in fasting TG from baseline at 3-, 6-, and 12-month endpoints), safety, and PK (e.g., C_{trough}) measures will be evaluated using graphical analysis and statistical analysis. These analyses will be either conducted and included in the study report, or data pooled and analyzed from all available Phase 2 and 3 studies and reported separately.

11. INVESTIGATOR'S REGULATORY OBLIGATIONS

11.1 Informed Consent

The written informed consent document should be prepared in the language(s) of the potential patient population, based on an English version provided by the Sponsor.

Before a patient's participation in the trial, the Investigator is responsible for obtaining written informed consent from the patient after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific qualification procedures or any Study Drug are administered. The patient must be given sufficient time to consider whether to participate in the study.

The acquisition of informed consent and the patient's agreement or refusal to notify his/her primary care physician should be documented in the patient's medical records and the informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion (not necessarily an Investigator). The original signed

informed consent form should be retained in the Study Master File and in any other locations required by institutional policy, and a copy of the signed consent form should be provided to the patient.

11.2 Ethical Conduct of the Study

The Guidelines of the World Medical Association (WMA) Declaration of Helsinki dated October 2002 the applicable regulations and guidelines of current Good Clinical Practice (GCP) as well as the demands of national drug and data protection laws and other applicable regulatory requirements will be strictly followed.

11.3 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent form, other written patient information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by the Sponsor before recruitment of patients into the study and shipment of volanesorsen. A copy of the written approval of any other items/materials that must be approved by the Study Center or IEC/IRB must also be received by the Sponsor before recruitment of patients into the study and shipment of Study Drug. The Investigator's Brochure must be submitted to the IEC/IRB for acknowledgement.

The Investigator must submit to and, where necessary, obtain approval from the IEC/IRB, for all subsequent protocol amendments and changes to the informed consent document. The Investigator should notify the IEC/IRB of deviations from the protocol in accordance with ICH GCP Section 4.5.2. The Investigator should also notify the IEC/IRB of serious adverse events occurring at the Study Center and other adverse event reports received from the Sponsor, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study. Copies of the Investigator's reports, all IEC/IRB submissions and the IEC/IRB continuance of approval must be sent to the Sponsor.

11.4 Patient Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained. On the case report forms (CRF) or other documents submitted to the Sponsor, patients should be identified by unique initials and a patient study number only. Documents that are not for submission to the Sponsor (e.g., signed informed consent forms) should be kept in strict confidence by the Investigator.

In compliance with Federal and local regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the patient to permit named representatives to have access to his/her study-related records without violating the confidentiality of the patient.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments

Protocol amendments must be made only with the prior approval of the Sponsor. Agreement from the Investigator must be obtained for all protocol amendments and amendments to the informed consent document. The regulatory authority and IEC/IRB must be informed of all amendments and give approval for any amendments likely to affect the safety of the patients or the conduct of the trial. The Investigator **must** send a copy of the approval letter from the IEC/IRB to the Sponsor.

12.2 Study Termination

The Sponsor reserves the right to terminate the study according to the terms of the site contract. The Investigator reserves the right to terminate their participation in the study, according to the terms of the site contract. The Investigator/Sponsor should notify the IEC/IRB in writing of the trial's completion or early termination and send a copy of the notification to the Sponsor.

12.3 Study Documentation and Storage

An electronic case report form (eCRF) utilizing an Electronic Data Capture (EDC) application will be used for this study.

The Investigator should ensure that all appropriately qualified persons to whom he/she has delegated trial duties are recorded on a Sponsor-approved Delegation of Site Responsibilities Form.

Source documents are original documents, data, and records from which the patient's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, imaging, and correspondence. In this study, CRFs may not be used as source documents.

The Investigator and Study Center staffs are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation in accordance with Section 8 of the ICH Guidelines (E6), suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Elements should include:

- Patient files containing completed CRFs, informed consents, and supporting copies of source documentation
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation and all correspondence to and from the IEC/IRB and the Sponsor
- If volanesorsen supplies are maintained at the Study Center, proof of receipt, volanesorsen Accountability Record, Return of volanesorsen for Destruction, final study volanesorsen reconciliation, and all volanesorsen-related correspondence

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

No study document should be destroyed without prior written agreement between the Sponsor or and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor.

12.4 Study Monitoring

The Sponsor representative and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the trial (e.g., CRFs and other pertinent data) provided that patient confidentiality is respected.

The Sponsor monitor is responsible for inspecting the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to patient medical records and other study-related records needed to verify the entries on the CRFs.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's Clinical Quality Assurance Department. Inspection of Study Center facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the trial conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

To ensure the quality of clinical data a clinical data management review will be performed on patient data received by the Sponsor. During this review, patient data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or Study Center notifications will be sent to the Study Center for completion and return to Sponsor.

The Principal Investigator will sign and date the indicated places on the CRF. These signatures will indicate that the principal Investigator inspected or reviewed the data on the CRF, the data queries, and the Study Center notifications, and agrees with the content.

12.5 Language

Case report forms must be completed in English. Generic names for concomitant medications should be recorded in English if possible, unless it is a combination drug, then record the trade name in English.

All written information and other material to be used by patients and investigative staff must use vocabulary and language that are clearly understood.

12.6 Compensation for Injury

The Sponsor maintains appropriate insurance coverage for clinical trials and will follow applicable local compensation laws. Patients will be treated and/or compensated for any study-related illness/injury in accordance with the information provided in the Compensation for Injury section of the Informed Consent document.

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14. APPENDICES

Appendix A Schedule of Procedures

Qualification through Treatment Period

Post-Treatment Follow-up

Appendix A Schedule of Procedures – Qualification through Treatment Period

Study Period		Qual[a]	Treatment Period																					
Study Week		-2 to -1	Wk 1		Wk 4	Wk 6	Wk 8	Wk 10	Month 3		Wk 15 & 17	Wk 19	Wk 21 & 23	Month 6		Wk 28 & 30	Wk 32	Wk 34 & 36	Wk 38	Wk 40 & 42	Wk 44	Wk 46 & 48	Month 12	
									Wk 12	Wk 13				Wk 25	Wk 26								Wk 50	Wk 52 or ET
Study Day		-14 to -7	1	2	22	36	50	64	78	85	99 & 113	127	141 & 155	169	176	190 & 204	218	232 & 246	260	274 & 288	302	316 & 330	344	358
Visit Window+/- Days		0	0	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Informed Consent		X																						
Outpatient Visit		X	X	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X	X[j]	X[j]	X[j]	X[j]	X	X[j]	X[j]	X[j]	X	X[j]	X[j]	X[j]	X[j]	X
Inclusion/Exclusion Criteria		X																						
Medical History[q]		X																						
Vital Signs + body weight (+ height on Day 1 only)		X	X		X		X			X					X				X					X
Physical Examination		X	X							X					X				X					X
12- lead ECG (triplicate)		X								X					X				X					X
MRI (liver/spleen)		X																						X[k]
Echocardiography		X													X[k]									X[k]
Blood Draw (Fasting)[c]	Chemistry Panel	X	X		X		X			X		X			X		X		X		X			X
	CBC with Differential[b]	X	← Platelets are assessed each calendar week, visits do not have specified windows to allow flexibility of scheduling. → X																					
	Serum Lipid Panel	X	X		X		X		X	X				X	X				X				X	X
	Blood viscosity[r]		X							X					X									X
	Platelet aggregation[r]	X	X							X					X									X
	Coagulation (aPTT, PT, INR)	X					X			X					X				X					X
	hsCRP, HbA1c, FPG, and de-lipidated free glycerol	X[n]	X							X					X									X
	Sedimentation Rate		X							X					X									X
	Complement (C5a, Bb)		X							X					X									X
	Plasma PK - Volanesorsen		X[l]	X	X		X			X					X				X					X
	Anti-Volanesorsen Antibodies		X		X		X			X					X				X					X
	FSH (women only, if applicable)	X																						
	Serum Pregnancy Test[d]	X			X		X			X		X			X		X		X		X			X
	Archived Serum & Plasma Samples[e]		X				X			X					X									X
	Troponin I[o]	X																						
	Platelet Bound Autoantibodies[r]		X																					
	Archive blood sample for potential gene sequencing related to hypertriglyceridemia (Group 2 if not available from index study)[g]	X																						

Appendix A Schedule of Procedures - Qualification through Treatment Period *Continued*

Study Period	Qual[a]	Treatment Period																					
Study Week	-2 to -1	Wk 1		Wk 4	Wk 6	Wk 8	Wk 10	Month 3		Wk 15 & 17	Wk 19	Wk 21 & 23	Month 6		Wk 28 & 30	Wk 32	Wk 34 & 36	Wk 38	Wk 40 & 42	Wk 44	Wk 46 & 48	Month 12	
								Wk 12	Wk 13				Wk 25	Wk 26								Wk 50	Wk 52 or ET
Study Day	-14 to -7	1	2	22	36	50	64	78	85	99 & 113	127	141 & 155	169	176	190 & 204	218	232 & 246	260	274 & 288	302	316 & 330	344	358
Visit Window+/- Days	0	0	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Urinalysis[c]	X	X^m		X		X			X^m		X^m			X^m		X^m		X^m		X^m			X^m
Fundus Photography[f]	X																						X^k
Genetic testing for FCS diagnosis (if not available in medical history)[g]	X																						
Weekly Study Drug: SC Injection		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Symptom Diary (weekly)	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Assessment(s)		X							X					X									X
Food/Drink Diary (quarterly)[h]		X							X					X									X
Diet/Alcohol Counseling[i]	X	X		X		X			X					X				X					X
Adverse Events	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Appendix A Schedule of Procedures – Post-Treatment Follow-up

Study Period		Post Treatment Follow-up[p]				
Study Week		Wk 54 & 56	Wk 58	Wk 65	Wk 71	Wk 78
Study Day		372 & 386	400	449	491	540
Visit Window+/- Days		2	7	7	7	7
Informed Consent						
Outpatient Visit		X[j]	X[j]	X	X[j]	X
Inclusion/Exclusion Criteria						
Vital Signs + body weight (+ height on Day 1 only)				X		X
Physical Examination				X		X
12- lead ECG (triplicate)				X		X
MRI (liver/spleen)						
Echocardiography						
Blood Draw (Fasting)[c]	Chemistry Panel		X	X	X	X
	CBC with Differential[b]	X[s]	X	X	X	X
	Serum Lipid Panel			X		X
	Coagulation (aPTT, PT, INR)					
	hsCRP, HbA1c, FPG, and de-lipidated free glycerol			X		X
	Sedimentation Rate			X		X
	Complement (C5a, Bb)			X		X
	Plasma PK - Volanesorsen			X		X
	Anti-Volanesorsen Antibodies			X		X
	FSH (women only, if applicable)					
	Serum Pregnancy Test[d]		X	X	X	X
	Archived Serum & Plasma Samples[e]			X		X
	Troponin I[o]					

Appendix A Schedule of Procedures – Post-Treatment Follow-up *Continued*

Study Period	Post Treatment Follow-up[p]				
Study Week	**Wk 54 & 56**	**Wk 58**	**Wk 65**	**Wk 71**	**Wk 78**
Study Day	**372 & 386**	**400**	**449**	**491**	**540**
Visit Window+/- Days	**2**	**7**	**7**	**7**	**7**
Urinalysis[c]		X[m]	X[m]	X[m]	X[m]
Fundus Photography[f]					
Genetic testing for FCS diagnosis (if not available in medical history)[g]					
Weekly Study Drug: SC Injection					
Symptom Diary (weekly)	X	X	X	X	X
Quality of Life Assessment(s)			X		X
Food/Drink Diary (quarterly)[h]			X		X
Diet/Alcohol Counseling[i]		X	X	X	X
Adverse Events	X	X	X	X	X
Concomitant Medication	X	X	X	X	X

Appendix A Schedule of Procedures *Continued*

a Qualification procedures performed (Please refer to Sections 3.4, 4.1, and 6.1.2)

b Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1 week and the result must be reviewed by the Investigator and confirmed to be acceptable before dosing can continue. All platelet count results will be promptly reviewed by the Investigator to determine if the count has met a stopping rule, or the dose reduction rule of 100,000/mm^3, or the dose pause rule of 75,000/mm^3. Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor

c Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours. During treatment period urine and blood samples will be collected prior to Study Drug administration. Does not apply to 24-hour PK blood draw

d Females of childbearing potential only

e Serum and plasma samples will be collected and stored for follow-up exploration of laboratory findings and/or adverse events (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.) in this or subsequent clinical studies of volanesorsen

f If possible, fundus photography should be completed prior to administration of the first dose of Study Drug (Group 2 ISIS 304801-CS16 roll over patients) and repeated at Week 52 (Please refer to Section 6.2.2.2)

g Genetic testing can be conducted for study Qualification (Group 2 ISIS 304801-CS16 roll over patients); genetic testing will only be conducted if allowed in the geographic region and only after the patient has given specific written informed consent for genetic testing

h In addition to diary, patients will be contacted at random times during the study to review their current eating and drinking habits

i To reinforce compliance to the diet and alcohol restrictions. Random diet/alcohol assessments (phone visits) will also be performed by dietician or study personnel

j Assessments and procedures to be conducted by either a home healthcare nurse, or the Study Center as arranged by the Study Center personnel

k A ± 7-day window is allowed for MRI, echocardiography procedures and fundus photography

l Full or abbreviated PK profile (see Appendix C)

m Expanded urinalysis (see Appendix B)

n HbA1c only

o All abnormal troponin samples will be rerun at the central laboratory and also analyzed for CK-MB

p If needed, the post-treatment follow-up period will be extended (with patients monitored every 6 weeks) until apoC-III levels return to baseline values

q Patient charts will be reviewed in order to collect data for events of acute pancreatitis or suspected pancreatitis in the patient's medical history. Chart review may be conducted at any time during the study. These events will be adjudicated in the same manner as for events of pancreatitis during the study

r May be done. Blood viscosity and platelet aggregation in volanesorsen-treatment naïve patients only

s Platelets are assessed each calendar week, visits do not have specified windows to allow flexibility of scheduling

Appendix B List of Laboratory Analytes

Appendix B List of Laboratory Analytes

Based on emerging data from this or future studies, additional tests not listed below may be performed on stored samples to better characterize the profile of volanesorsen or other similar oligonucleotides.

Clinical Chemistry Panel

- Sodium
- Potassium
- Chloride
- Bicarbonate
- Total protein
- Albumin
- Calcium
- Magnesium
- Phosphorus
- Glucose
- BUN
- Creatinine
- Uric Acid
- Total bilirubin
- Direct (conjugated) bilirubin
- Indirect (unconjugated) bilirubin
- ALT
- AST
- Alkaline phosphatase

Coagulation

- aPTT (sec)
- PT (sec)
- INR

Lipid Panel

- Total Cholesterol
- LDL-C
- HDL-C
- Triglycerides
- Non-HDL-C
- VLDL-C
- apoA-1
- apoB
- apoC-III

Hematology

- Red blood cells
- Hemoglobin
- Hematocrit
- MCV, MCH, MCHC
- Platelets
- White blood cells
- WBC Differential (% and absolute)
  - Neutrophils
  - Eosinophils
  - Basophils
  - Lymphocytes
  - Monocytes

Pharmacokinetics[1] & Immunogenicity

- Volanesorsen levels in plasma
- Anti-volanesorsen antibodies in plasma

Other Assessments

- hsCRP
- Sedimentation Rate
- C5a, Bb
- Troponin I[2]
- CK-MB[2]
- Platelet Bound Autoantibodies[3]
- De-lipidated free glycerol
- HbA1c, FPG
- Blood viscosity[3]

Urinalysis

- Color
- Appearance
- Specific gravity
- pH
- Protein
- Blood
- Ketones
- Urobilinogen
- Glucose
- Bilirubin
- Leukocyte esterase
- Nitrate
- Microscopic examination[4]

Additional Measures for Expanded Urinalysis

- Total protein (quantitative)
- Microalbumin
- β2-microglobulin

Platelet Function

- Platelet aggregation[3]

1 Plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, IM testing (or possibly for purposes of IM assay development and/or validation), or to assess other actions of volanesorsen with plasma constituents

2 All abnormal troponin samples will be rerun at the central laboratory and also analyzed for CK-MB

3 May be done

4 Will be performed on abnormal findings unless otherwise specified

Appendix C Pharmacokinetic Sampling Schedule

Appendix C Pharmacokinetic Sampling Schedule

Blood samples for the determination of plasma volanesorsen concentrations will be collected prior to dosing, and at various times throughout the dosing and post-treatment follow-up period as noted in the tables below.

PK Sampling Schedule (All Patients except PK Subgroup)

Week	Wk 1	Wk 4	Wk 8	Wk 13	Wk 26	Wk 38	Wk 52	Wk 65	Wk 78
Study Day	**D1**	**D22**	**D50**	**D85**	**D176**	**D260**	**D358**	**D449**	**D540**
Visit Window +/- Days	0	2	2	2	2	3	2	7	7
Time Point	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime	Anytime

PK Sampling Schedule (PK Subgroup only*)

Week	Wk 1	Wk 1	Wk 4	Wk 8	Wk 13	Wk 26	Wk 38	Wk 52	Wk 65	Wk 78
Study Day	**D1**	**D2**	**D22**	**D50**	**D85**	**D176**	**D260**	**D358**	**D449**	**D540**
Visit Window +/- Days	0	0	2	2	2	2	3	2	7	7
Time Point	Pre-dose, 1, 2, 3, 4, 6, 8, and 12 hrs post-dose	24 hrs Post-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime	Anytime

* Patients at selected sites will be asked to participate in the extended 24-hour PK profile beginning on Study Day 1. Participation is optional

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

The following grading recommendations for adverse events relating to lab test abnormalities are based upon the **Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010**

Adverse Event	Mild	Moderate	Severe
Hematology			
aPTT prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage
Eosinophils increased†	650 – 1,500 cell/mm^3	1,501 - 5,000 cell/mm^3	>5,000 cell/mm^3
Fibrinogen decreased	<1.0 - 0.75 x LLN or <25% decrease from baseline	<0.75 - 0.5 x LLN or 25 - <50% decrease from baseline	<0.5 x LLN or ≥50% decrease from baseline
Hemoglobin decreased (Anemia)	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated
Hemoglobin increased	Increase in >0 - 2 g/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 g/dL above ULN or above baseline if baseline is above ULN	Increase in >4 g/dL above ULN or above baseline if baseline is above ULN
INR increased	>1 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation
Lymphocyte count decreased	<LLN - 800/mm^3; <LLN - 0.8 x 10^9/L	<800 - 500/mm^3; <0.8 - 0.5 x 10^9 /L	<500 /mm^3; <0.5 x 10^9 /L
Lymphocyte count increased	-	>4000/mm^3 - 20,000/mm^3	>20,000/mm^3
Neutrophil count decreased	<LLN - 1500/mm^3; <LLN - 1.5 x 10^9 /L	<1500 - 1000/mm^3; <1.5 - 1.0 x 10^9 /L	<1000/mm^3; <1.0 x 10^9 /L
Platelet count decreased	<LLN - 75,000/mm^3; <LLN - 75.0 x 10^9 /L	<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9 /L	<50,000/mm^3; <50.0 x 10^9 /L
White blood cell decreased	<LLN - 3000/mm^3; <LLN - 3.0 x 10^9 /L	<3000 - 2000/mm^3; <3.0 - 2.0 x 10^9 /L	<2000/mm^3; <2.0 x 10^9 /L
Chemistry			
Acidosis	pH <normal, but >=7.3	-	pH <7.3
Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Alkalosis	pH >normal, but ≤7.5	-	pH >7.5
Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 x ULN
Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

Adverse Event	Mild	Moderate	Severe
Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer
CD4 lymphocytes decreased	<LLN - 500/mm^3; <LLN - 0.5 x 10^9 /L	<500 - 200/mm^3; <0.5 - 0.2 x 10^9 /L	<200/mm^3; <0.2 x 10^9 /L
CPK increased*	>ULN - <6 ULN	6 - 10 x ULN	>10 x ULN
Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 x ULN
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 mg/dL; >3.1 mmol/L; Ionized calcium >1.6 mmol/L; hospitalization indicated
Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 mg/dL; >13.9 mmol/L; hospitalization indicated
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0; hospitalization indicated
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 mg/dL; >1.23 mmol/L
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 mmol/L; hospitalization indicated
Hyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 mg/dL; <1.75 mmol/L; Ionized calcium <0.9 mmol/L; hospitalization indicated
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 mg/dL; <3.0 mmol/L	<40 mg/dL (<2.2 mmol/L) AND requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions‡
Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 mmol/L; hospitalization indicated
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 mg/dL; <0.4 mmol/L
Hyponatremia	<LLN - 130 mmol/L	-	<130 mmol/L
Hypophosphatemia	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 mg/dL; <0.6 mmol/L
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

Adverse Event	Mild	Moderate	Severe
Urine			
Proteinuria Adults Children	1+ proteinuria; urinary protein <1.0 g/24 hrs -	2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs; Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Urinary protein ≥3.5 g/24 hrs; Urine P/C >1.9
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated

†Grading for this parameter is derived from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007

*Grading for this parameter is derived from the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0, Nov 2014

‡Modified for consistency with the ADA and Endocrine Society Guidelines (Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. Diabetes Care 2013;36:1384-95)

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ISIS 304801-CS7

The APPROACH Open-Label Study

Volanesorsen (ISIS 304801)

An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol Amendment 7 – 7 April 2017

EudraCT No: 2015-003755-21

ISIS 304801-CS7

The APPROACH Open-Label Study

Volanesorsen (ISIS 304801)

An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol Amendment 7 – 7 April 2017

Protocol History:

Original Protocol:	28 August 2015
Protocol Amendment 1:	2 February 2016
Protocol Amendment 2:	22 April 2016
Protocol Amendment 3:	9 May 2016
Protocol Amendment 4:	6 June 2016
Protocol Amendment 5:	6 July 2016
Protocol Amendment 6:	18 November 2016

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Ionis Protocol Number: ISIS 304801-CS7

Protocol Amendment 7

EudraCT No: 2015-003755-21

Clinical Phase: 3

The APPROACH Open-Label Study

Volanesorsen (ISIS 304801)

An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

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Date: 7 April 2017

Confidentiality Statement

This document contains confidential information of Ionis Pharmaceuticals, Inc., that must not be disclosed to anyone other than the recipient study staff and members of the independent ethics committee, institutional review board, or authorized regulatory agencies. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc.

Protocol Signature Page

Protocol Number:	ISIS 304801-CS7
Protocol Title:	An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Amendment:	Amendment 7
Date:	7 April 2017

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)", dated 7 April 2017, and agree to conduct the study as described herein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice (E6).

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc.

Investigator's Signature

Investigator's Name *(please print)*

Date (DD Month YYYY)

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PROTOCOL AMENDMENT

Protocol Number: ISIS 304801-CS7

Protocol Title: An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Amendment Number: 7

Amendment Date: 7 April 2017

The purpose of this protocol amendment is to implement the following modifications to Protocol ISIS 304801-CS7 Amendment 6 dated 18 November 2016:

1. To update the platelet safety monitoring rules shown in Table 3.
2. To add LPL activity of ≤ 20% of normal in medical history as an inclusion criteria for Group 2 and 3 patients as has been allowed for Group 1 patients.
3. To add platelet count < lower limit of normal (LLN) for the central laboratory (i.e., < 140,000/mm^3) for Group 3 patients.
4. To assess acute pancreatitis in medical history in Group 2 patients.
5. Added archive blood sample for potential gene sequencing related to hypertriglyceridemia (Group 3; Group 2 if not available from index study)
6. Added blood viscosity (may be done) to assess potential benefit of ISIS 304801 administration and platelet aggregation (may be done) to assess platelet function.

Minor changes (not included in the list of changes below) have been made throughout the protocol to correct errors and/or to improve the overall clarity of the original protocol but these changes do not impact subject safety, exposure, or the overall study design.

The following table provides a summary list of major changes to the protocol, additions are indicated as underline and deletions are indicated as strikethrough:

Protocol Section	Description of Change	Rationale
Section 3.4.4 Post-Treatment	**Was** The post-treatment evaluation period is 13 weeks and consists of 4 Study Center visits on Weeks 54, 56, 58, and 65 (Weeks 54, 56, and 58 may be conducted by a home healthcare nurse). **Is** The post-treatment evaluation period is 13 weeks and consists of 7 Study Center visits on Weeks 53, 54, 55, 56, 57, 58, and 65 (Weeks 53, 54, 55, 56, 57, and 58 may be conducted by a home healthcare nurse).	To provide added patient safety regarding platelet count reductions and ISIS 304801 dose exposure

Protocol Section	Description of Change	Rationale
Synopsis Section 5.1 Inclusion Criteria	3. Groups 1 and 2: Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement. Groups 2 and 3: Patients must also meet the following criteria in order to enter into the open-label Study: a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L) b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) **supported** by documentation of **at least 1** of the following: • Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1) • **Post heparin plasma LPL activity of ≤ 20% of normal in medical history. Note: testing of LPL activity should not be performed to confirm eligibility for the study** c. Group 2: Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 index study Group 3: Fasting TG ≥ 750 mg/dL at Screening for this open-label study	To add LPL activity of ≤ 20% of normal in medical history as an inclusion criteria for Group 2 and 3 patients as has been allowed for Group 1 patients
Synopsis 5.2 Exclusion Criteria for Group 3	5. Any of the following laboratory values at Screening a. Hepatic: • Total bilirubin > upper limit of normal (ULN), unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL • ALT > 2.0 x ULN • AST > 2.0 x ULN b. Renal: • Persistently positive (2 out of 3 consecutive tests ≥ 1+) for protein on urine dipstick. In the event of a positive test eligibility may be confirmed by a quantitative total urine protein measurement of < 500 mg/24 hrs • Persistently positive (2 out of 3 consecutive tests ≥ trace positive) for blood on urine dipstick. In the event of a positive test eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field • Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault < 50 mL/min (MDRD or CKD-EPI formulas can be used instead of Cockcroft-Gault for estimation of GFR in patients with low body weight after discussion with Sponsor Medical Monitor) **c. Platelet count < lower limit of normal (LLN) for the central laboratory (i.e., < 140,000/mm^3)** d~~c~~. Cardiac Troponin I > ULN at Screening e~~d~~. LDL-C > 130 mg/dL at Screening f~~e~~. Any other laboratory abnormalities which, in the opinion of the Investigator or the Sponsor, would make the patient unsuitable for inclusion	To provide added patient safety regarding platelet count reductions, and ISIS 304801 dose exposure

Protocol Section	Description of Change	Rationale
Synopsis 6.1.3 Treatment Period	During the treatment period, patients will report to the study center for clinic visits a minimum of 5 times during Weeks 1-52 (see Schedule of Procedures in Appendix A). Study Drug will be administered once weekly unless the patient is on a biweekly dosing schedule for safety reasons (Section 8.1). Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), AEs, concomitant medication/procedure information, lipid panel, **blood viscosity,** volanesorsen plasma concentrations, immunogenicity (IM) testing, **platelet aggregation**, liver/spleen MRI, ECGs, echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Adverse events at the injection site should be collected as adverse events. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period and all patients will complete a daily food diary for one week prior to their quarterly visit. All blood and urine samples should be collected prior to volanesorsen administration. Blood sampling at Weeks 2, **3**, 4, **5**, 6, **7**, 8, **9**, 10, **11,** 12, **14**, 15, **16**, 17, **18**, 19, **20**, 21, **22**, 23, **24**, 25, **27**, 28, **29**, 30, **31**, 32, **33**, 34, **35**, 36, **37, 39**, 40, **41**, 42, ~~**43**~~, 44, **45**, 46, **47**, 48, **49,** 50, and **51** may be conducted by a home healthcare nurse. Approval for study procedures to be conducted by a home healthcare nurse on other outpatient visit days will require prior approval by the Sponsor. Patients must be fasted prior to drawing all blood samples and samples drawn locally should also be sent to the central laboratory for analysis whenever possible. ~~Every effort should be made to ensure the previous week's dose is given 7 days prior to a scheduled clinic visit.~~ Dosing instructions and training will be provided to the patient where applicable.	To provide added patient safety regarding platelet count reductions and ISIS 304801 dose exposure
6.14 Extended Treatment Period	During the extended treatment period, patients will report to the study center for clinic visits during Weeks 54-104 (see Schedule of Procedures in Appendix A). Study Drug will be administered once weekly unless the patient is on a biweekly dosing schedule for safety reasons (Section 8.1). Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), AEs, concomitant medication/procedure information, lipid panel, volanesorsen plasma concentrations, IM testing, ECGs, and physical examinations will be performed according to the Schedule of Procedures in Appendix A. Adverse events at the injection site should be collected as adverse events. Dietary counseling will be reinforced at intervals throughout the extended treatment period. All blood and urine samples should be collected prior to volanesorsen administration. Blood sampling at Weeks **53**, 54, **55**, 56, **57**, 58, **59**, 60, **61**, 62,**63, 65**, 66, **67**, 68, **69**, 70, **71**, 72, **73**, 74, **75, 77**, 78, **79**, 80, **81**, 82, **83**, 84, **85**, 86, **87**, 88, **89, 91**, 92, **93**, 94, **95**, 96, **97**, 98, **99**, 100, **101**, 102, and **103** may be conducted by a home healthcare nurse. Approval for study procedures to be conducted by a home healthcare nurse on other outpatient visit days will require prior approval by the Sponsor. Patients must be fasted prior to drawing all blood samples and samples drawn locally should also be sent to the central laboratory for analysis whenever possible. ~~Every effort should be made to ensure the previous week's dose is given 7 days prior to a scheduled clinic visit.~~ Dosing instructions and training will be provided to the patient where applicable.	To provide added patient safety regarding platelet count reductions and ISIS 304801 dose exposure

Protocol Section	Description of Change	Rationale
6.1.6 Post-Treatment Period	After completion of the Week 52 visit assessments, patients will have the option of participating in an expanded access program or continuing dosing for up to an additional 52 weeks until an expanded access program is approved and available in their country as described in Section 6.1.4. Patients not participating in an expanded access program will enter the 13-week post treatment evaluation period. This 13-week post treatment evaluation period consists of **7** Study Center visits on Weeks **53**, 54, **55**, 56, **57**, and 58 (which may be conducted by a home healthcare nurse), and Week 65 as outlined in the Schedule of Procedures in Appendix A. Patients who complete, or terminate early from, the extended treatment period without subsequently participating in an expanded access program will enter a 13-week post treatment evaluation period consisting of **7** Study Center visits on Weeks **105**, 106, **107**, 108, **109**, and 110 (which may be conducted by a home healthcare nurse), and Week 117 as outlined in the Schedule of Procedures in Appendix A.	To provide added patient safety regarding platelet count reductions and ISIS 304801 dose exposure
6.2.1 Laboratory Assessments	Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1-week **and the result must be reviewed by the Investigator and confirmed to be acceptable before dosing can continue. All platelet count results will be promptly reviewed by the Investigator to determine if the count has met a stopping rule, or the dose reduction rule of 100,000/mm^3,** ~~and determined not to have met a stopping rule before dosing can continue~~ **or the dose pause rule of 75,000/mm^3**. ~~If there is no reportable platelet count within 14 days of the last platelet count, the Investigator will contact the patient to hold dosing until a new platelet count is obtained and reviewed.~~ ~~All platelet count results will be promptly reviewed by the Investigator to ensure that the count has not met the stopping rule and to determine whether the rate of decline is suggestive that the patient could be approaching the dose pause rule of 75,000/mm^3.~~ Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor.	To provide added patient safety regarding platelet count reductions, ISIS 304801 dose exposure, and treatment recommendations
6.2.10 Chart Review for Incidents of Acute Pancreatitis in Medical History	**Added** 6.2.10 Chart Review for Incidents of Acute Pancreatitis in Medical History (Group **2 and** 3)	To assess acute pancreatitis in medical history in Group 2 patients
8.1 Volanesorsen Administration	**Removed** ~~Every effort should be made to ensure the previous week's dose is given 7 days prior to a scheduled clinic visit.~~	Dosing recommendations provided in updated monitoring and drug administration updates

Protocol Section	Description of Change	Rationale
8.5.2 Safety Monitoring for Platelet Count Results	Actions to be taken in the event of reduced platelet count are shown in Table 3 in Section 8.6.3. **Monitor every 1 week unless otherwise specified.** **Study Drug administration is contingent on the availability of the immediately preceding test result. An interpretable platelet value must be available within 7 days prior to dosing. Only the study doctor or qualified designee can authorize continued Study Drug administration based on an acceptable platelet value. Patients should not administer a dose until they have been contacted by their study doctor or designee and told that it is acceptable to dose. Authorization to dose must be documented in the patient's medical records.** **Due to the 1 to 2-year study duration it is anticipated that patients may undertake travel including vacations, which may impede weekly platelet monitoring. In some situations, it may be possible to arrange for local laboratory testing or use of the home healthcare service at their temporary location. The intent is to maintain weekly platelet monitoring and dosing where possible, as well as Investigator site contact with the study patients. However, if the above options are not possible, a temporary interruption of study treatment will be planned with a prompt blood draw upon the patient's return which must be reported and reviewed by the Investigator prior to the patient resuming dosing.** The tests outlined in Table 2 should also be performed as soon as possible. Additional lab tests will be determined by the Sponsor Medical Monitor or designee in consultation with the Investigator. Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor (See also Stopping Rules Section 8.6.3).	To provide added patient safety regarding platelet count reductions, ISIS 304801 dose exposure, and treatment recommendations

<table>
<tr><th>Protocol Section</th><th>Description of Change</th><th>Rationale</th></tr>
<tr><td>8.5.2 Safety Monitoring for Platelet Count Results
Continued</td><td>Table 2 Labs to Be Performed in the Event of a Platelet Count <u>Less than the Lower Limit of Normal (x2) or < 100,000/mm^3 (x1)*</u><s>< 75,000/mm^3</s>
<u>*In patients who have any 2 occurrences (consecutive or non-consecutive) of platelet count less than the lower limit of normal or who have any 1 occurrence of platelets < 100,000/mm^3. Labs only need to be performed once. Labs may be collected over multiple visits, if blood requirements are a concern, as per Investigator discretion.</u>
Note: The following labs may change as additional data is assessed, and sites will be updated regarding any changes.
<table>
<tr><td>To Be Performed at Local Lab</td></tr>
<tr><td>Peripheral smear (should be performed locally, fixed and sent to central lab for review)</td></tr>
<tr><td>Fibrinogen split products or D-dimer on fresh blood</td></tr>
<tr><td>To Be Performed at Central Lab</td></tr>
<tr><td>Citrated sample for platelets</td></tr>
<tr><td>Coagulation panel (PT/INR, aPTT)</td></tr>
<tr><td>CBC with reticulocytes</td></tr>
<tr><td><u>Folate (folic acid)</u></td></tr>
<tr><td><u>Vitamin B12</u></td></tr>
<tr><td>Fibrinogen</td></tr>
<tr><td>von Willebrand factor</td></tr>
<tr><td>Total globulins, total IgA, IgG and IgM</td></tr>
<tr><td>Complement: total C3, total C4, Bb, C5a</td></tr>
<tr><td>hsCRP</td></tr>
<tr><td><u>Helicobacter pylori (breath test)</u></td></tr>
<tr><td>Serology for:</td></tr>
<tr><td>HBV, HCV, HIV (if not done recently for screening)</td></tr>
<tr><td>Rubella</td></tr>
<tr><td>CMV</td></tr>
<tr><td>EBV</td></tr>
<tr><td>Parvo B19</td></tr>
<tr><td><s>Helicobacter pylori (IgG serum test)</s></td></tr>
<tr><td>Auto-antibody screen:</td></tr>
<tr><td>Antiphospholipid</td></tr>
<tr><td>Rheumatoid factor</td></tr>
<tr><td>Anti-dsDNA</td></tr>
<tr><td>Anti-thyroid</td></tr>
<tr><td>To Be Performed at Specialty Lab(s)</td></tr>
<tr><td>Antiplatelet antibodies and Anti-PF4 assay</td></tr>
<tr><td>Anti-ASO antibody</td></tr>
</table></td><td>To provide added patient safety regarding platelet count reductions, ISIS 304801 dose exposure, and treatment recommendations</td></tr>
</table>

Protocol Section	Description of Change	Rationale
Section 8.6.3 Stopping Rules for Platelet Count Results	Actions to be taken in the event of a low platelet count are summarized in Table 3 below. In the event of a platelet count less than 75,000/mm^3 that is associated with major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with volanesorsen will be stopped permanently. The follow-up schedule for any events meeting this stopping criterion will be determined by the Investigator in consultation with the Sponsor Medical Monitor. In the event of any platelet count less than ~~25~~50,000/mm^3, or a platelet count less than 75,000/mm^3 that occurs while the patient is on dosing at 300 mg every 2 weeks ~~or 150 mg every week~~ then dosing of a patient with volanesorsen will be stopped permanently. Platelet count will be monitored as outlined in Table 3. ~~daily until 2 successive values show improvement then monitored every 2-3 days until platelet count is stable.~~ Administration of steroids is recommended for patients whose platelet count is less than ~~25~~50,000/mm^3. Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5 2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (note: may require continuation with oral steroids after methylprednisolone). Triglyceride levels will be monitored weekly, and AE monitoring will continue, during cortiscosteroid treatment and the laboratory alert will be changed from an increase of 2,000 to 500 mg/dL during that period. In the event of a platelet count less than 75,000/mm^3, and in the absence of major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with volanesorsen should be suspended temporarily until the platelet count has recovered to > 100,000/mm^3. If dosing is continued it should be at a reduced dose frequency of 300 mg every 2 weeks ~~or a reduced dose of 150 mg per week~~ (refer to Section 8.7). The suitability of the patient for continued dosing will be determined by the Investigator in consultation with the Study Medical Monitor and will be based on factors such as the original rate of decline in the patient's platelet count, whether any bleeding events were experienced by the patient, and the speed of recovery of platelet count upon holding of dosing. If after the first dosing rechallenge the platelet count again falls below 75,000/mm^3, then dosing of the patient with Study Drug will be stopped permanently. ~~Following a rechallenge platelet count should be tested every week until count is stable.~~ ~~Any unreportable platelet count result must be rechecked and determined not to have met a stopping rule before dosing can continue.~~ ~~If there is no reportable platelet count within 14 days of the last platelet count, the Investigator will contact the patient to hold dosing until a new platelet count is obtained and reviewed.~~	To provide added patient safety regarding platelet count reductions, ISIS 304801 dose exposure, and treatment recommendations

<table>
<tr><th>Protocol Section</th><th>Description of Change</th><th>Rationale</th></tr>
<tr><td>Section 8.6.3 Stopping Rules for Platelet Count Results</td><td>
Was:
Table 3 Actions in Patients with Low Platelet Count
<table>
<tr><th>Platelet Count on Rx</th><th>Drug Dose</th><th>Monitoring</th></tr>
<tr><td>Normal range, > 140K/mm^3</td><td>No action</td><td>Monitor every 2 weeks</td></tr>
<tr><td>100K-140K/mm^3</td><td>No action</td><td>Closer observation
Monitor every 1 week until stable*</td></tr>
<tr><td>75K-100K/mm^3</td><td>Permanently reduce dose frequency to 300 mg every 2 weeks or reduce dose to 150 mg weekly</td><td>Closer observation
Monitor every 1 week</td></tr>
<tr><td>50K-75K/mm^3</td><td>If occurs while on dose of 300 mg every 2 weeks or 150 mg every week then permanently discontinue Study Drug, otherwise dose pause.
When platelet count returns to > 100K/mm^3 restart dosing at dose frequency of 300 mg every 2 weeks or 150 mg weekly only if approved by Sponsor Medical Monitor</td><td>Closer observation
Monitor every 2-3 days until 2 successive values show improvement
Consider discontinuation of antiplatelet agents/NSAIDS/ anticoagulant medication</td></tr>
<tr><td>25K-50K/mm^3</td><td>If occurs while on dose of 300 mg every 2 weeks or 150 mg every week then permanently discontinue Study Drug, otherwise dose pause.
When platelet count returns to > 100K/mm^3 restart dosing at dose frequency of 300 mg every 2 weeks or 150 mg weekly only if approved by Sponsor Medical Monitor</td><td>Closer observation
Monitor daily until 2 successive values show improvement then monitor every 2-3 days until platelet count stable
Discontinue antiplatelet agents/NSAIDS/anticoagulant medication while platelet count < 50K/mm^3 if possible</td></tr>
</table>
</td><td>To provide added patient safety regarding platelet count reductions, ISIS 304801 dose exposure, and treatment recommendations</td></tr>
</table>

<table>
<tr><th>Protocol Section</th><th>Description of Change</th><th>Rationale</th></tr>
<tr><td>Section 8.6.3 Stopping Rules for Platelet Count Results Continued</td><td>Was Continued

Table 3 Actions in Patients with Low Platelet Count Continued
<table>
<tr><th>Platelet Count on Rx</th><th>Drug Dose</th><th>Monitoring</th></tr>
<tr><td>< 25K/mm^3</td><td>Permanently discontinue Study Drug</td><td>Closer observation:
Monitor daily until 2 successive values show improvement then monitor every 2-3 days until platelet count stable
Steroids recommended**
Consider need for hospitalization and referral to hematologist
Discontinue antiplatelet agents/NSAIDS/anticoagulant medication while platelet count < 50K/mm^3 if possible</td></tr>
</table>
* At least 3 consecutive values measured weekly that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3
** Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (note: may require continuation with oral steroids after methyl prednisolone)</td><td></td></tr>
</table>

<table>
<tr><th>Protocol Section</th><th>Description of Change</th><th>Rationale</th></tr>
<tr><td>Section 8.6.3 Stopping Rules for Platelet Count Results
Continued</td><td>Is

Table 3 Actions in Patients with Low Platelet Count or Drop in Platelet Count
<table>
<tr><th>Platelet Count on Rx</th><th>Drug Dose</th><th>Monitoring</th></tr>
<tr><td></td><td>Study Drug administration is contingent on the availability of the immediately preceding test result. An interpretable platelet value must be available within 7 days prior to dosing. Only the study doctor or qualified designee can authorize continued Study Drug administration based on an acceptable platelet value. Patients should not administer a dose until they have been contacted by their study doctor or designee and told that it is acceptable to dose. Authorization to dose must be documented in the patient’s medical records.</td><td>Monitor every 1 week unless otherwise specified
Obtain additional lab tests (Table 2) if 2 occurrences consecutive or non-consecutive) of platelet count 140K - > 100K/mm^3 or 1 occurrence of platelet count ≤ 100K/mm^3. Labs only need to be performed once. Labs may be collected over multiple visits, if blood requirements are a concern, as per Investigator discretion.</td></tr>
<tr><td>> 100K/mm^3</td><td>Weekly 300 mg Study Drug administration</td><td></td></tr>
<tr><td>100K/mm^3 - > 75K/mm^3</td><td>Permanently reduce dose frequency to 300 mg every 2 weeks</td><td></td></tr>
<tr><td>75K/mm^3 - > 50K/mm^3</td><td>• If occurs while on dose of 300 mg every 2 weeks then permanently discontinue Study Drug, otherwise dose pause
• When platelet count returns to > 100K/mm^3 restart dosing at dose frequency of 300 mg every 2 weeks only if approved by Sponsor Medical Monitor</td><td>• Monitor every 2-3 days until 2 successive values are >75K/mm^3 then monitor every 1 week
• Consider discontinuation of antiplatelet agents/NSAIDS/ anticoagulant medication</td></tr>
</table></td><td>To provide added patient safety regarding platelet count reductions, ISIS 304801 dose exposure, and treatment recommendations</td></tr>
</table>

<table>
<tr><th>Protocol Section</th><th>Description of Change</th><th>Rationale</th></tr>
<tr><td>Section 8.6.3 Stopping Rules for Platelet Count Results Continued</td><td>Table 3 Actions in Patients with Low Platelet Count or Drop in Platelet Count Continued
<table>
<tr><th>Platelet Count on Rx</th><th>Drug Dose</th><th>Monitoring</th></tr>
<tr><td>≤ 50K/mm^3</td><td>Permanently discontinue Study Drug</td><td>• Monitor daily until 2 successive values show improvement then monitor every 2-3 days until 2 successive values are > 75K/mm^3 then monitor every 1 week
• Patient should be evaluated by a hematologist to provide diagnostic and therapeutic management
• Steroids recommended*. It is strongly recommended that, unless the patient has a medical contraindication to receiving glucocorticoids, the patient receives glucocorticoid therapy to reverse the platelet decline.
• Monitor triglyceride levels weekly and continue AE monitoring during steroid therapy
• Discontinue antiplatelet agents/ NSAIDS/ anticoagulant medication while platelet count is< 50K/mm^3 if possible</td></tr>
</table>
* Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or methylprednisolone 30 mg/kg/day for 7 days (note: may require continuation with oral steroids after methylprednisolone)</td><td>To provide added patient safety regarding platelet count reductions, ISIS 304801 dose exposure, and treatment recommendations</td></tr>
<tr><td>9.4.1 Serious Adverse Events</td><td>In the interest of patient safety, and in order to fulfill regulatory requirements, all SAEs (regardless of their relationship to volanesorsen) should be reported to the Sponsor or designee within 24 hours of the Study Center's first knowledge of the event. The collection of SAEs will begin after the patient signs the informed consent form and stop at the end of the patient's follow-up period which is defined as the Week 65 visit (or Week 117 if patient enters the extended treatment period). When the Investigator is reporting by telephone, it is important to speak to someone in person versus leaving a message. An Initial Serious Adverse Event Form should be completed and a copy should be faxed to the Sponsor or designee.</td><td>To provide consistent SAE reporting rules</td></tr>
</table>

Protocol Section	Description of Change	Rationale
Synopsis 10.1.1 Efficacy Endpoints	• Percent change and absolute change from baseline in fasting TG • Frequency and severity of patient reported abdominal pain during the treatment period • Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-HDL-C, apoB, HDL-C, apolipoprotein A-1 (apoA-1), VLDL-C, and LDL-C • Percent change from baseline in fasting total apolipoprotein C-III • **Change in blood viscosity (may be evaluated)** • Quality of Life questionnaires (EQ-5D, SF-36) • Adjudicated acute pancreatitis event rate • Other symptoms: eruptive xanthoma, lipemia retinalis	To assess potential benefit of ISIS 304801 administration
Synopsis 10.1.2 Safety Endpoints	• Adverse events including adjudicated events of pancreatitis and MACE • Vital signs and weight • Physical examinations • Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis) • Echocardiography • Electrocardiograms (ECGs) • Use of concomitant medications • MRIs • **Platelet aggregation (may be evaluated)**	To assess platelet function following ISIS 304801 administration
Appendix A	Removed Week 2.5 CBC with Differential c Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1 week and the result must be reviewed by the Investigator and confirmed to be acceptable ~~and determined not to have met a stopping rule~~ before dosing can continue~~. If there is no reportable platelet count within 14 days of the last platelet count, the Investigator will contact the patient to hold dosing until a new platelet count is obtained and reviewed~~. All platelet count results will be promptly reviewed by the Investigator to ~~ensure that~~ determine if the count has ~~not~~ met ~~the~~ a stopping rule, ~~and to determine whether the rate of decline is suggestive that the patient could be approaching the~~ or the dose reduction rule of 100,000/mm^3, or the dose pause rule of 75,000/mm^3. Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor Added: Blood Viscosity and Platelet Aggregation e May be done. Blood viscosity and platelet aggregation in volanesorsen-treatment naïve patients only Added: Archive blood sample for potential gene sequencing related to hypertriglyceridemia (Group 3; Group 2 if not available from index study)	To provide added patient safety regarding platelet count reductions, ISIS 304801 dose exposure, and treatment recommendations. Blood viscosity and potential gene sequencing to assess potential benefit of ISIS 304801 administration. Platelet aggregation to assess platelet function following ISIS 304801 administration.
Appendix B	Added Blood Viscosity and Platelet Aggregation	To assess potential benefit of ISIS 304801 administration To assess platelet function following ISIS 304801 administration

PROTOCOL SYNOPSIS

Protocol Title	An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Study Phase	3
Indication	Familial Chylomicronemia Syndrome
Study Objectives	To evaluate the safety and efficacy of dosing and extended dosing with volanesorsen (volanesorsen sodium 300 mg) in patients with FCS
Study Design	This is a multi-center open-label study of: Group 1: ISIS 304801-CS6 (index study) roll-over FCS patients Group 2: ISIS 304801-CS16 (index study) roll-over FCS patients Group 3: FCS patients who did not participate in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies All patients will receive volanesorsen 300 mg once per week for 52 weeks. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period. Following the Week 52 visit, patients will have the option of participating in an expanded access program or continuing dosing for up to an additional 52 weeks until an expanded access program is approved and available in their country. Patients not participating in an expanded access program will enter a 13-week post-treatment evaluation period
Number of Patients	Up to approximately 70 patients dosed
Study Population	Inclusion Criteria: 1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law 2. Age ≥ 18 years at time of informed consent 3. Groups 1 and 2: Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement. Groups 2 and 3: Patients must also meet the following criteria in order to enter into the open-label study: a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L) b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) supported by documentation of at least 1 of the following: • Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1) • Post heparin plasma LPL activity of ≤ 20% of normal in medical history. Note: testing of LPL activity should not be performed to confirm eligibility for the study c. Group 2: Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 index study Group 3: Fasting TG ≥ 750 mg/dL at Screening for this open-label study 4. Able and willing to participate in a 65-week study

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	Inclusion Criteria: *Continued* 5. Satisfy 1 of the following: a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved), abstinent*, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration b. Males: Surgically sterile, abstinent* or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration * Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception Exclusion Criteria for Group 1 (ISIS 304801-CS6) and Group 2 (ISIS 304801-CS16) Index Study Roll-over Patients 1. Have any new condition or worsening of existing condition which in the opinion of the Investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study 2. Unwilling to comply with lifestyle requirements for the duration of the study (Section 6.3) Exclusion Criteria for Group 3 (patients who did not participate in an index study) 1. Diabetes mellitus with any of the following: a. Newly diagnosed within 12 weeks of screening b. HbA1c ≥ 9.0% at Screening c. Recent change in anti-diabetic pharmacotherapy (change in dosage or addition of new medication within 12 weeks of screening [with the exception of ± 10 units of insulin]) d. Anticipated need to change dose or type of medication during the treatment period of the Study (with the exception of ± 10 units of insulin) e. Current use of GLP-1 agonists 2. Severe hypertriglyceridemia other than due to familial chylomicronemia syndrome 3. Active pancreatitis within 4 weeks prior to screening

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	Exclusion Criteria for Group 3 (patients who did not participate in an index study) *Continued* 4. History within 6 months of screening of acute or unstable cardiac ischemia (myocardial infarction, acute coronary syndrome, new onset angina), stroke, transient ischemic attack or unstable congestive cardiac failure requiring a change in medication or major surgery within 3 months of screening 5. Any of the following laboratory values at Screening a. Hepatic: • Total bilirubin > upper limit of normal (ULN), unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL • ALT > 2.0 x ULN • AST > 2.0 x ULN b. Renal: • Persistently positive (2 out of 3 consecutive tests ≥ 1+) for protein on urine dipstick. In the event of a positive test eligibility may be confirmed by a quantitative total urine protein measurement of < 500 mg/24 hrs • Persistently positive (2 out of 3 consecutive tests ≥ trace positive) for blood on urine dipstick. In the event of a positive test eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field • Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault < 50 mL/min (MDRD or CKD-EPI formulas can be used instead of Cockcroft-Gault for estimation of GFR in patients with low body weight after discussion with Sponsor Medical Monitor) c. Platelet count < lower limit of normal (LLN) for the central laboratory (i.e., < 140,000/mm^3) d. Cardiac Troponin I > ULN at Screening e. LDL-C > 130 mg/dL at Screening f. Any other laboratory abnormalities which, in the opinion of the Investigator or the Sponsor, would make the patient unsuitable for inclusion 6. Uncontrolled hypertension (BP > 160/100 mm Hg) 7. History of bleeding diathesis or coagulopathy or clinically-significant abnormality in coagulation parameters at Screening 8. History of heart failure with NYHA greater than Class II 9. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1 10. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B 11. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated 12. Treatment with another investigational drug, biological agent, or device within 1 month of screening, or 5 half-lives of investigational agent, whichever is longer

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	Exclusion Criteria for Group 3 (patients who did not participate in an index study) *Continued* 13. Unwilling to comply with lifestyle requirements (Section 6.3) 14. Use of any of the following: a. Statins, omega-3 fatty acids (prescription and OTC), or fibrates unless on a stable dose for at least 3 months prior to screening and dose and regimen expected to remain constant during the treatment period. Patients taking OTC omega-3 fatty acids should make every effort to remain on the same brand throughout the study b. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to screening c. Systemic corticosteroids or anabolic steroids within 6 weeks prior to screening unless approved by the Sponsor Medical Monitor d. Atypical antipsychotic medications (e.g., olanzapine and clozapine) unless on a stable dose for at least 3 months prior to screening and dose and regimen expected to remain stable throughout the study e. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to screening and dose and regimen expected to remain constant during the treatment period f. Glybera gene therapy within 2 years prior to screening g. Oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, and apixaban) unless on a stable dose for at least 4 weeks prior to screening and regular clinical monitoring is performed h. Tamoxifen, estrogens or progestins unless on a stable dose for at least 4 months prior to screening and dose and regimen expected to remain constant during the treatment period i. Plasma apheresis within 4 weeks prior to screening or planned during the study j. Prior exposure to ISIS 304801 k. Any other medication unless stable at least 4 weeks prior to screening (Occasional or intermittent use of over-the-counter medications will be allowed at Investigator's discretion) 15. Blood donation of 50 to 499 mL within 30 days of screening or of > 499 mL within 60 days of screening 16. Known hypersensitivity to any of the excipients of the Study Drug (ISIS 304801 or placebo) 17. Have any other conditions, which, in the opinion of the Investigator or the Sponsor would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the study
Treatment Group	Volanesorsen 300 mg once per week
Study Drug Administration	Volanesorsen will be administered as subcutaneous (SC) injections.
Dose Adjustments	Dose adjustments, including dose interruptions and/or decreasing the dose frequency will be allowed for safety or tolerability after consultation with the Sponsor Medical Monitor.

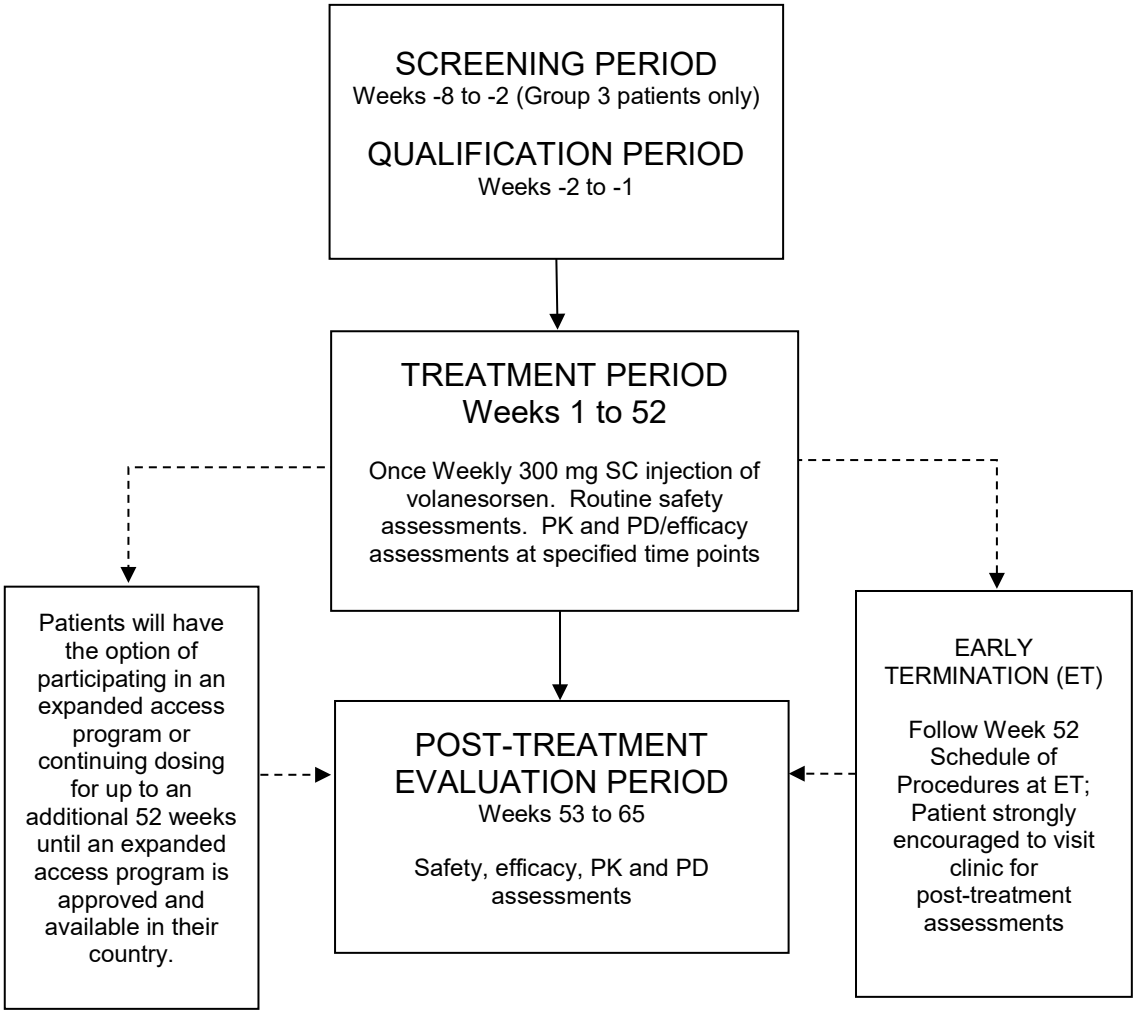
PROTOCOL SYNOPSIS *Continued*

Rationale for Dose and Schedule Selection	The dose of 300 mg once weekly was chosen for the double-blinded placebo-controlled Phase 3 index studies (ISIS 304801-CS6 and ISIS 304801-CS16) based on the pharmacodynamic and safety analysis of the Phase 2 studies (Section 2.4) which included a subset of patients with FCS. The same dose of 300 mg once weekly will be used in this open-label study of FCS patients.
Study Visit Schedule and Procedures	The study for an individual patient will generally consist of the following periods: • Group 1 and 2 patients (participated in ISIS 304801-CS6 or ISIS 304801-CS16 index study): A qualification period of up to 2 weeks (unless approved by the Sponsor). Please refer to Section 4.1 and Appendix A • Group 3 patients (did not participate in an index study): An up to 8-week screening and qualification period, including a diet stabilization period of at least 6 weeks (screening and diet stabilization period may be reduced, per Sponsor approval, if the patient is following a diet for optimal control of TGs and disease management prior to screening). Please refer to Section 6.1.2 and Appendix A • All patients: o A 52-week treatment period during which volanesorsen will be administered as a once weekly SC injection o Option to participate in an extended treatment period (up to an additional 52 weeks) o A 13-week post-treatment evaluation period or expanded access program The patients, Investigators, study staff, and the Sponsor will remain blinded to lipid data through the last patient's Week 13 visit of the open-label study or until results from the database locks for the ISIS 304801-CS6 and ISIS 304801-CS16 index studies becomes available, whichever comes first. Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), adverse events (AE), concomitant medication/procedure information, lipid panel, blood viscosity, volanesorsen plasma concentrations, immunogenicity (IM) testing, platelet aggregation, liver/spleen magnetic resonance imaging (MRI), ECGs, echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Dietary counseling will be repeated at intervals throughout the treatment and follow-up period and a daily food/drink diary will be completed for the week prior to each quarterly visit by each patient. Following the Week 52 visit, patients will have the option of participating in an expanded access program or continuing dosing for up to an additional 52 weeks until an expanded access program is approved and available in their country. Patients not participating in an expanded access program will enter the 13-week post-treatment evaluation period.

PROTOCOL SYNOPSIS *Continued*

Safety and Tolerability Evaluations	Overall safety and tolerability of volanesorsen will be assessed by determining the incidence and severity of adverse and serious adverse events (including independently adjudicated events of acute pancreatitis and MACE), withdrawals due to adverse events, and changes in laboratory and other safety parameters.
Planned Analyses	Safety Endpoints: • Adverse events including adjudicated events of acute pancreatitis and MACE • Vital signs and weight • Physical examinations • Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis) • Echocardiography • Electrocardiograms (ECGs) • Use of concomitant medications • MRIs • Platelet aggregation (may be evaluated) Efficacy Endpoints: • Percent change and absolute change from baseline in fasting TG • Frequency and severity of patient reported abdominal pain during the treatment period • Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-high-density lipoprotein-cholesterol (non-HDL-C), apolipoprotein B [apoB], high-density lipoprotein-cholesterol (HDL-C), apolipoprotein A-1 [apoA-1], very-low-density lipoprotein-cholesterol (VLDL-C), and LDL-C • Percent change from baseline in fasting total apolipoprotein C-III (apoC-III) • Change in blood viscosity (may be evaluated) • Quality of Life questionnaires (EQ-5D, SF-36) • Adjudicated acute pancreatitis event rate • Other symptoms: eruptive xanthoma, lipemia retinalis
Pharmacokinetic Evaluations	Plasma samples will be taken from all patients for the measurement of volanesorsen as follows: trough levels (pre-dose) throughout treatment and post-treatment levels during the post-treatment follow-up period. In a subset of patients, more frequent assessment of plasma concentrations of volanesorsen will be performed to determine volanesorsen pharmacokinetic parameters. Plasma sample collection time points are detailed in Appendix A and Appendix C.
Statistical Considerations	No sample size calculations were performed as this is an open-label study.
Sponsor	Ionis Pharmaceuticals, Inc.
Collaborator	Akcea Therapeutics

STUDY DESIGN AND TREATMENT SCHEMA



STUDY GLOSSARY

Abbreviation/Acronym	Definition
ADA	anti-drug antibody
AE	adverse Event
ALP	alkaline Phosphatase
ALT	alanine Aminotransferase
ANA	antinuclear Antibody
apoA-1	apolipoprotein A-1
apoB	apolipoprotein B
apoC-III	apolipoprotein C-III
apoE	apolipoprotein E
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
CBC	complete blood count
C_{max}	maximum observed drug concentration
CRF	case report form
DNA	deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
ET	early termination
FAS	full analysis set
FCS	Familial Chylomicronemia Syndrome
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
GPIHBP1	glycosylphosphatidylinositol-anchored hdl-binding protein 1
HAPI	heritability and phenotype intervention
HbA1c	glycated hemoglobin
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein-cholesterol
hsCRP	High-sensitivity C-reactive protein
ICH	International Conference on Harmonization
IDL	intermediate density lipoprotein
IEC	Independent Ethics Committee
IM	immunogenicity
Index Studies	ISIS 304801-CS6 and ISIS 304801-CS16

INR	International Normalized Ratio
IRB	Institutional Review Board
IXRS	Interactive Voice/Web-Response System
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein-cholesterol
LMF1	lipase maturation factor 1
LPL	lipoprotein lipase
MACE	major acute cardiovascular event
MOE	2′-*O*-(2-methoxyethyl)
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NCS	not clinically-significant
NOAEL	no-observed-adverse-effect level
non-HDL-C	non-high-density lipoprotein-cholesterol
OTC	over the counter
PFS	prefilled syringe
PD	pharmacodynamic
PK	pharmacokinetic
PPS	per protocol set
PT	prothrombin time
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SUSAR	suspected unexpected serious adverse reaction
T2DM	type 2 diabetes mellitus
T_{max}	time to maximal concentration
TG	triglycerides
Treatment-emergent	occurring after first dose of Study Drug
TRL	triglyceride-rich lipoproteins
ULN	upper limit of normal
VLDL	very-low-density lipoprotein
VLDL-C	very-low-density lipoprotein-cholesterol
VLDL-TG	lipoprotein-triglyceride
WMA	World Medical Association

1. OBJECTIVES

The objective of the study is to evaluate the safety and efficacy of dosing and extended dosing with volanesorsen in patients with familial chylomicronemia syndrome.

2. BACKGROUND AND RATIONALE

2.1 Overview of Disease

Familial Chylomicronemia Syndrome (FCS) is an inherited disease characterized by severe hypertriglyceridemia and chylomicronemia, and risk or history of pancreatitis. It is a rare autosomal recessive disease that can be diagnosed either in childhood or adulthood.

Fasting plasma triglyceride (TG) levels in FCS patients are typically 10-fold to 100-fold above normal (1,500 to 15,000 mg/dL), despite extreme dietary fat restriction (20 g or approximately 15-20% of daily calorie intake) (Brunzell 1999-2011). Patients with FCS often present in infancy or childhood with frequent and severe abdominal pain, repetitive colicky pain, repeated episodes of potentially fatal acute pancreatitis, and failure to thrive (Brunzell 1999-2011; Tremblay et al. 2011). Physical examination frequently reveals eruptive xanthomas, lipemia retinalis and hepatosplenomegaly, and plasma from patients appears lactescent, interfering with determination of other laboratory parameters (Tremblay et al. 2011).

Patients with fasting triglyceride levels > 10 mmol/L probably have a component of chylomicronemia. Clinical diagnosis would include evidence of clinical features of chylomicronemia syndrome and secondary causes such as uncontrolled type 1 or type 2 diabetes mellitus (T2DM), hypothyroidism, poor diet, alcohol use, nephrotic syndrome or use of associated medications should be ruled out. The diagnosis of FCS may be made more specifically by genotyping or confirmation of very low or absent lipoprotein lipase (LPL) enzyme activity in post heparin plasma (Brunzell 1999-2011).

Patients with FCS carry a heavy burden of medical complications, the most serious, as described above, being an extreme risk of recurrent and potentially fatal pancreatitis. Due to the recurrent episodes of acute pancreatitis, these patients may also develop chronic pancreatitis and signs of exocrine or endocrine pancreatic insufficiency, including diabetes mellitus (Gaudet et al. 2013). While the pathophysiology underlying chylomicron-related pancreatitis has not been completely elucidated, 1 hypothesis is that large chylomicrons lodged in pancreatic capillaries are exposed to pancreatic lipase, with the subsequent release of free fatty acids through the hydrolysis of chylomicron-associated TGs. High concentrations of free fatty acids are thought to damage pancreatic cells leading to emergent pancreatitis (Yang et al. 2009; Berglund et al. 2012).

The etiology of extreme hypertriglyceridemia in FCS is considered to be ineffective triglyceride clearance, due to an extremely low level of LPL activity. LPL normally functions to hydrolyze triglycerides (TG) in chylomicrons along the luminal surface of capillaries, mainly in heart, skeletal muscle, and adipose tissue, promoting triglyceride clearance from the circulation. LPL is regulated by a number of key genes, and loss-of-function mutations in one of these genes, or the LPL gene itself, results in FCS (Surendran et al. 2012). In addition to loss of function mutations, null mutations, and nonsense mutations in the LPL gene, other genes currently identified in FCS patients, and known to directly influence LPL activity include: apolipoprotein C-II (APOC2) a cofactor for LPL (Schuster et al. 2011); apolipoprotein A-V

(APOA5) an enhancer of LPL activity (Schaap et al. 2004); lipase maturation Factor 1 (LMF1), a transmembrane protein involved in LPL maturation (Doolittle et al. 2009); glycosylphosphatidylinositol-anchored HDL-binding protein 1 (GPIHBP1), a capillary endothelial cell protein that provides a platform for LPL-mediated processing of chylomicrons (Beigneux et al. 2007).

2.2 Therapeutic Rationale

Apolipoprotein C-III (ApoC-III), a key regulator of plasma triglyceride levels, is a 79 amino acid glycoprotein synthesized principally in the liver (Ooi et al. 2008; Figure 1). ApoC-III is a major regulator of lipoprotein metabolism and plays a pivotal role in regulating plasma TG levels (Chan et al. 2008). It is a component of triglyceride-rich lipoproteins (TRLs) and a potent inhibitor of LPL (Lemieux et al. 2003). At higher concentrations apoC-III also inhibits hepatic lipase activity (Kinnunen and Ehnolm 1976), an enzyme which plays an important role in the conversion of dense very-low-density lipoprotein (VLDL) to intermediate density lipoprotein (IDL) and to LDL (Mendivil et al. 2010), as well as in the remodeling of HDL (Brown et al. 2010). In addition, increased apoC-III content adversely affects apoE-mediated hepatic uptake of TG-rich remnants (Mann et al. 1997). Thus, elevated plasma apoC-III levels are associated with impaired hydrolysis and retarded clearance of TG-rich particles, resulting in the accumulation of lipoprotein-triglyceride (VLDL-TG) and chylomicrons in plasma and the development of hypertriglyceridemia (Ito et al. 1990).

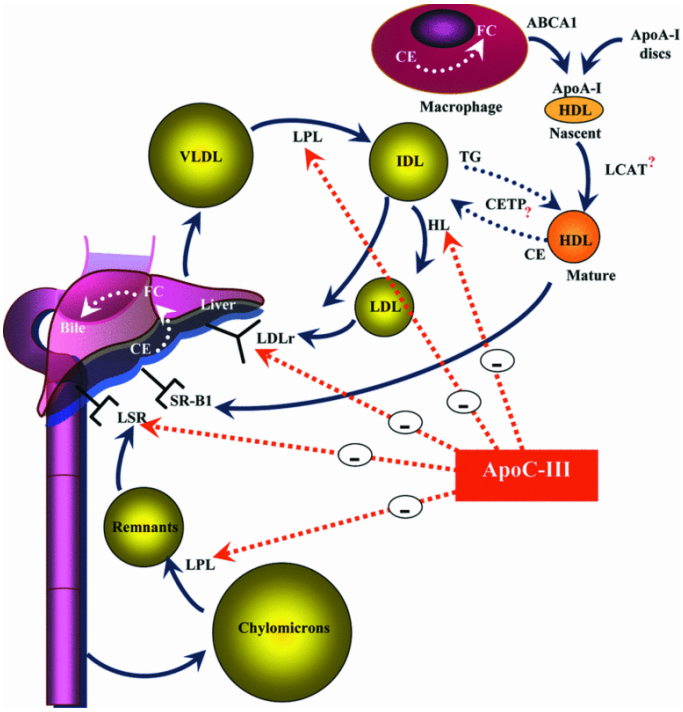


Figure 1 ApoC-III Regulates Lipoprotein Metabolism by Multiple Mechanisms

From Ooi et al. 2008; ABCA1 = ATP-binding cassette A1, apo = apolipoprotein, CE = cholesterol ester, CETP = cholesterol ester transfer protein, FC = free cholesterol, HDL = high-density lipoprotein, HL = hepatic lipase, IDL = intermediate-density lipoprotein, LCAT = lecithin cholesterol acyltransferase, LDL = low-density lipoprotein, LDLr = LDL receptor, LPL = lipoprotein lipase, LSR = lipolysis-stimulated receptor, SR-B1 = scavenger receptor B-1, TG = triglyceride, VLDL = very low-density lipoprotein.

Mechanistically, FCS is primarily a consequence of ineffective clearance of TRL. ApoC-III is a prominent component of TRL (e.g., VLDL and chylomicrons). In addition to its role in inhibiting LPL, apoC-III inhibits TRL remnant (TG-depleted remnant lipoprotein) uptake by hepatic lipoprotein receptors by steric inhibition of the interaction of apoE with these receptors.

Human genetic data have demonstrated positive phenotypic associations with loss (e.g., null or nonsense mutations) and negative effects with gain of function mutations (Atzmon et al. 2006; Pollin et al. 2008; Petersen et al. 2010). A novel nonsense mutation in the apoC-III gene was identified in the heritability and phenotype intervention (HAPI) heart study in Old Order Amish that results in lower plasma apoC-III and TG levels and lower LDL-C, increased HDL-C and reduced atherosclerosis (Pollin et al. 2008). In another study involving a group of 214 Ashkenazi Jews of advanced age (had passed or nearly reached 100 years of age), genotype analysis revealed a polymorphism in the apoC-III gene (APOC3-641CC genotype) with a clear pattern of age-dependent frequency that was associated with significantly lower levels of apoC-III protein, a favorable lipoprotein profile and increased longevity (Atzmon et al. 2006). In contrast to the Amish and Ashkenazi apoC-III polymorphisms associated with lower plasma TG, apoC-III polymorphisms associated with higher plasma TG have also been recently described (Petersen et al. 2010). In a cohort of lean (mean body mass index [BMI] = 24.7 ± 3.6 kg/m^2) Asian Indians, carriers of apoC-III variant alleles (C-482T, T-455C, or both) were noted to have significantly higher plasma apoC-III and TG levels, and decreased ability to clear postprandial plasma TG from the circulation. Taken together, the available data strongly support the development of a therapy that reduces plasma apoC-III levels in order to reduce the very high circulating triglyceride and chylomicron levels that are accompanied by increasing risk for acute pancreatitis.

Given the profound reductions in TGs observed with volanesorsen treatment in FCS patients who have no detectable LPL activity (See Section 2.3.4), and the mechanistic data available to date on apoC-III function, potential mechanisms that explain how apoC-III inhibition results in triglyceride reduction in FCS patients include: (1) enhancing the very small residual amounts of LPL activity that these patients may have, below the limit of detection of the assay in many cases (2) potentially enhanced activity of other lipases also involved in the metabolism and breakdown of TGs, such as hepatic lipase or endothelial lipase (Kinnunen and Ehnolm 1976), and (3) apoC-III interaction with Apolipoprotein E (apoE), an important factor in liver reuptake of lipid particles by blocking apoE-mediated uptake of lipid particles in the liver (Breyer et al. 1999), and therefore, reducing apoC-III might enhance apoE-mediated uptake of lipid particles. Volanesorsen-mediated reduction of apoC-III could be contributing to one or all of these mechanisms resulting in the observed potent and sustained reductions in TG.

Through a novel apoC-III lowering mechanism of action, volanesorsen may provide the potential to manage triglyceride levels in FCS patients.

2.3 Volanesorsen

2.3.1 Mechanism of Action

Volanesorsen is a second-generation antisense oligonucleotide (ASO) drug targeted to human apoC-III. It is complementary to a region within the 3′ untranslated region of the apoC-III messenger ribonucleic acid (mRNA) and binds to the mRNA by Watson and Crick base pairing.

The hybridization (binding) of volanesorsen to the cognate mRNA, results in the RNase H1-mediated degradation of the apoC-III mRNA, thus preventing production of the apoC-III protein. Maximal antisense-mediated reduction of target mRNA levels is typically greater than 90% of control levels in sensitive tissues (Crooke and Bennett 1996; Zhang et al. 2010). Furthermore, reduction in target mRNA levels using this approach correlates directly with a subsequent reduction in target protein levels.

2.3.2 Chemistry

Chemically, volanesorsen is a synthetic oligomer of 20 nucleotides (i.e., a 20-mer) that are connected sequentially by phosphorothioate linkages. The nucleotide sequence of volanesorsen (Figure 2) is complementary to a 20-nucleotide stretch within the 3′ untranslated region of the apoC-III mRNA transcript at base position 489-508. Structurally, the oligonucleotide has 3 regions. Two (2) of them, the 5 nucleotides at the 5′ end and the 5 nucleotides at the 3′ end, are composed of 2′-*O*-(2-methoxyethyl) (MOE)-modified ribonucleotides. These MOE-modified nucleotides confer (1) increased affinity to the target mRNA (Altmann et al. 1996; McKay et al. 1999), (2) increased resistance to exonucleases and endonucleases (thereby increasing stability in tissue) (Geary et al. 2003), and (3) amelioration of some of the high dose toxicities thereby resulting in an improved safety profile compared to first generation antisense drugs containing phosphorothioate modified oligodeoxynucleotides (DNA) (Henry et al. 2000). The third region, the central portion of the oligonucleotide, is composed of 10 oligodeoxynucleotides. This chimeric design is called a MOE-Gapmer, and volanesorsen employs this chimeric structure to enable use of the RNase H1-mechanism for antisense activity. This is because while the 2′-MOE modification confers increased stability and affinity, it does not support RNase H1 catalysis of RNA hybridized to 2′-MOE-modified nucleotides (McKay et al. 1999). This is caused by conformational changes induced in the heteroduplex by 2′-alkoxy:RNA hybrids that are not recognized by RNase H1 enzymes (Inoue et al. 1987; Monia et al. 1993). By limiting the 2′-MOE modification to nucleotides flanking the phosphorothioate oligodeoxynucleotide core, the beneficial attributes of the 2′-MOE chemistry are preserved while also retaining RNase H1 recognition.

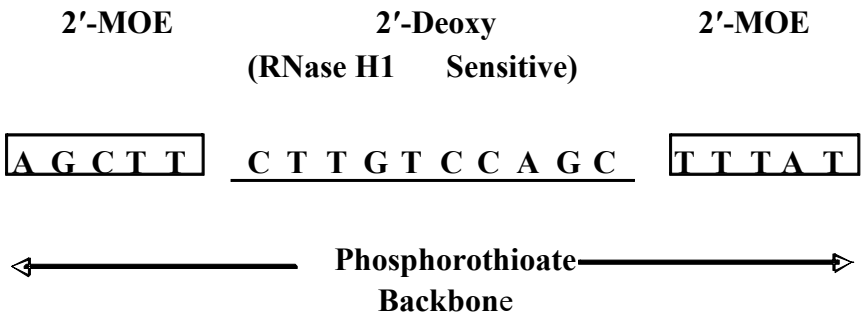


Figure 2 Design of Chimeric 2′-MOE Phosphorothioate Oligonucleotides (MOE-Gapmer). The sequence of volanesorsen is shown

2.3.3 Preclinical Experience

Inhibition of apoC-III using volanesorsen has been shown to potently reduce hepatic apoC-III mRNA as well as plasma apoC-III protein and TG in a dose- and time-dependent fashion in several species, including human apoC-III transgenic mice, and other rodent and monkey models. Treatment with volanesorsen also resulted in reduced VLDL and chylomicron TG and reduced postprandial TG in hypertriglyceridemic monkeys (Graham et al. 2013).

The pharmacokinetics (PK) and toxicity of volanesorsen have been assessed in mice, rats, and cynomolgus monkeys. General toxicity studies with volanesorsen for up to 39 weeks of treatment followed by up to a 20-week recovery period are complete. The preclinical toxicology program for volanesorsen consists of single dose safety pharmacology studies in the monkey (cardiovascular) and mouse (neurobehavioral and pulmonary assessment studies), *in vitro* and *in vivo* genetic toxicity assessment, repeat dose fertility and/or developmental reproductive toxicology studies in the mouse and rabbit and evaluation in the *in vitro* human Ether-á-go-go-related gene (hERG) assay.

Volanesorsen treatment-related findings in mice and monkeys were generally consistent with those expected for the 2′-MOE-class of ASOs. Treatment-related findings included effects consistent with drug accumulation in tissues in rodents and monkeys, species-dependent proinflammatory response in rodents and monkeys and complement activation and reductions in platelet counts in the monkey. In the mouse and monkey general toxicity studies, reduction of hepatic apoC-III mRNA (> 75%) was not associated with any findings that could be considered related to the pharmacologic inhibition of apoC-III for up to 39 weeks of treatment.

The long-term, chronic toxicology studies in rodents with volanesorsen produced a significant proinflammatory response that led to subsequent effects on the heart at high doses. The rodent species are most sensitive to the proinflammatory effects of antisense molecules. Importantly, these effects on the heart were not observed in the monkey chronic toxicity studies even at the highest doses tested where drug exposure was higher than that in rodents.

Because these changes were not observed in monkeys, the findings in the heart are considered to be rodent-specific and not relevant to humans. Nevertheless, such effects will be monitored by measurement of echocardiograms that will be included in this clinical study.

Volanesorsen caused no untoward effects in safety pharmacology studies (*in vitro* and *in vivo*) and was non-genotoxic (*in vitro* and *in vivo*). Volanesorsen had no effects on fertility or embryo/fetal development in the mouse or rabbit reproductive toxicity studies. In these studies, volanesorsen was detected in placental tissue but not in fetal tissue indicating that little, if any, drug was able to cross the placenta to reach the fetus. Reduction of apoC-III mRNA (64% in males and 47% in females) also did not affect fertility or cause untoward effects on embryo/fetal development in mice.

Detailed information concerning the preclinical studies conducted with volanesorsen can be found in the volanesorsen Investigator's Brochure.

2.3.4 Clinical Experience

Detailed information concerning the clinical studies conducted with volanesorsen can be found in the volanesorsen Investigator's Brochure. A summary is included below.

Volanesorsen has been evaluated in one Phase 1 study and two Phase 2 studies, all double blinded and placebo controlled. The total exposures comprise 99 patients and healthy volunteers administered volanesorsen from 50 to 400 mg subcutaneously up to 3 months (compared to 37 administered placebo).

All clinical trials of volanesorsen have shown large and clinically meaningful reductions in fasting plasma apoC-III and TG (~80% and 70%, respectively, mean reduction from baseline with 300 mg dose) with a very high degree of consistency of response between the different patient groups. This includes healthy volunteers, patients with moderate to severe hypertriglyceridemia not on background TG-lowering therapy, patients with moderate to severe hypertriglyceridemia on a background stable fibrate therapy (Gaudet et al. 2015), patients with FCS, and patients with T2DM.

In a Phase 2 study, 3 patients with FCS were treated with 300 mg/wk volanesorsen in an open-label fashion. These patients had a mean baseline fasting TG level of 1,844 mg/dL and all 3 patients achieved TG levels below or close to 500 mg/dL during the dosing period out to Day 92 (Figure 3). Two (2) of the FCS patients had an absolute reduction in fasting TG in excess of 1,500 mg/dL (Gaudet et al. 2014).

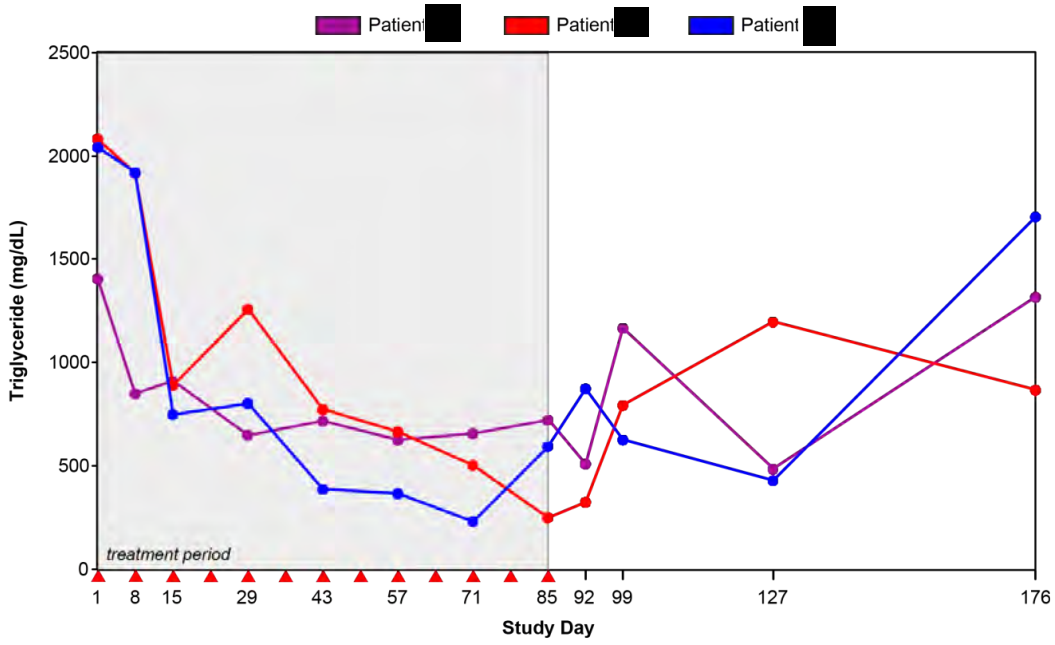


Figure 3 Fasting Triglycerides in Patients with FCS Treated with Volanesorsen

In clinical studies conducted to date volanesorsen has been well-tolerated and has shown a favorable safety profile. There has been no clinical or laboratory evidence of drug-drug interactions.

In the completed studies there have been no volanesorsen associated laboratory abnormalities suggestive of an effect on the renal (serum creatinine, proteinuria) or hepatic systems (alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin). In Phase 2 studies, there was a mild decrease of platelet count associated with volanesorsen administration that recovered in the post-treatment period and was not associated with platelet-related adverse events (AEs). In the blinded ongoing clinical trials of ISIS 304801, 2 patients of 142 dosed (as of February 29, 2016) had a decrease in platelet count to less than 50,000/mm^3 in the absence of major bleeding or clinically-relevant non-major bleeding and had Study Drug paused as per the monitoring and stopping rules for platelet counts (Section 8.6.3). Platelet counts recovered following suspension of dosing.

The most frequently observed AEs with volanesorsen were local reactions at the injection site. Local cutaneous reactions at the injection site defined as those events presenting as either pain, tenderness, erythema, pruritus or swelling occurring on the day of injection and persisting for at least 2 days were infrequent (~15% of injections), were almost always mild, resolved spontaneously, were non-progressive, and were not associated with systemic sequelae.

2.4 Rationale for Dose and Schedule of Administration

The dose and schedule selected for this study is 300 mg per week for 52 weeks. The dose of 300 mg per week is supported by both the cumulative nonclinical data available to date and the Phase 2 clinical data. In nonclinical studies, volanesorsen treatment-related effects in rodents and monkeys were consistent with drug accumulation in tissues and also include species-specific proinflammatory responses. In the monkey, the No-Observed-Adverse-Effect Level (NOAEL) was defined by the cumulative clinical pathology results and histopathology data which provide an adequate clinical margin. No nonclinical findings were considered to be related to the pharmacologic inhibition of apoC-III.

The safety data to date suggest that volanesorsen has been well-tolerated at dose levels up to 300 mg in patients with high triglycerides (including type 2 diabetes patients and administration in combination with fibrates and statins) with the most common AEs being local to the injection site and predominantly mild. A pooled analysis of safety for the Phase 2 studies did not demonstrate any clear difference in safety or tolerability between the different doses tested (100 mg, 200 mg, and 300 mg per week for 13 weeks).

Analysis of the cohorts in which volanesorsen was studied at different doses demonstrates dose-dependent pharmacology with respect to pharmacodynamic (PD) effect on the target, apoC-III, with a clear difference in the TG-lowering effect between the different doses in the 100 mg to 300 mg dose range as compared to placebo.

In addition to the nonclinical and clinical experience of volanesorsen, the dose and schedule of administration is supported by the preclinical and clinical safety experience of several other 2′-MOE-modified ASOs that have been safely administered intravenously and subcutaneously in multiple clinical studies at doses up to 1000 mg and for treatment durations that exceed 24 months (Santos et al. 2015).

3. EXPERIMENTAL PLAN

3.1 Study Design

This is an open-label study of:

Group 1: ISIS 304801-CS6 (index study) roll-over FCS patients

Group 2: ISIS 304801-CS16 (index study) roll-over FCS patients

Group 3: FCS patients who did not participate in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies

Up to approximately 70 patients will receive 300 mg once weekly volanesorsen for 52 weeks.

Following the Week 52 visit, patients will have the option of participating in an expanded access program or continuing dosing for up to an additional 52 weeks until an expanded access program is approved and available in their country. Patients not participating in an expanded access program will enter a 13-week post-treatment evaluation period.

3.2 Number of Study Centers

This study will be conducted at multiple centers worldwide.

3.3 Number of Patients

Up to approximately 70 patients will be dosed.

3.4 Overall Study Duration and Follow-up

The Study will consist of the following periods:

3.4.1 Group 1 and 2 Patients (participated in ISIS 304801-CS6 or ISIS 304801–CS16 index study): Qualification

A period of up to 2 weeks (unless approved by the Sponsor) is given to complete qualification assessments outlined in the Schedule of Procedures. Please refer to Section 4.1 and Appendix A.

3.4.2 Group 3 Patients (did not participate in an index study): Screening/Qualification

An up to 8-week screening and qualification period, including a diet stabilization period of at least 6 weeks (screening and diet stabilization period may be reduced, per Sponsor approval, if the patient is following a diet for optimal control of TGs and disease management prior to screening. Please refer to Section 6.1.2 and Appendix A.

3.4.3 Treatment

The treatment period is 52 weeks. Eligible patients will report to the Study Center for assessments at specified intervals throughout the 52-week treatment period as detailed in the Schedule of Procedures (Appendix A). During the treatment period, volanesorsen is administered by SC injection once weekly.

3.4.4 Post-Treatment

The post-treatment evaluation period is 13 weeks and consists of 7 Study Center visits on Weeks 53, 54, 55, 56, 57, 58, and 65 (Weeks 53, 54, 55, 56, 57, and 58 may be conducted by a home healthcare nurse).

3.5 End-of-Study

The End-of-Study is last patient, last visit.

3.6 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will review (as needed) safety, tolerability and efficacy data collected on volanesorsen during this study. Based on its ongoing assessment of the safety and tolerability of volanesorsen, the DSMB will provide recommendations to the Sponsor for modifying, stopping or continuing the study as planned. Details on the safety assessments, frequency of review and meeting schedules are outlined in the DSMB Charter and/or the statistical analysis plan (SAP).

4. PATIENT ENROLLMENT

4.1 Screening/Qualification

Before patients may be enrolled into the study, the Sponsor requires a copy of the Study Center's written independent ethics committee/institutional review board (IEC/IRB) approval of the protocol, informed consent form, and all other patient information.

Patients or their legally acceptable representatives must sign the consent form before any study-specific procedures or evaluations related to this open-label study are performed.

Groups 1 and 2 (Qualification): During the qualification period, the eligibility of the patient to enroll in the open-label study will be determined. Final assessments from the ISIS 304801-CS6 or ISIS 304801-CS16 studies may be used for qualification. A period of up to 2 weeks after completion of the ISIS 304801-CS6 or ISIS 304801-CS16 index studies (unless approved by the Sponsor) is given to complete qualification. Qualified patients will retain the unique patient identification number that was assigned to them during the ISIS 304801-CS6 or ISIS 304801-CS16 index studies. The patient identification number will be used to identify the patient throughout the extension trial and must be used on all study documentation related to that patient. The patient identification number must remain constant throughout the extension trial.

Group 3 (Screening and Qualification): At the time of consent, the patient will be considered enrolled into the study and will be assigned a unique screening number before any study procedures, including screening procedures, are performed. At the time of enrollment, patients will be assigned a unique patient identification number. This number will be used to identify the patient throughout the trial and must be used on all study documentation related to that patient. The screening number and patient identification number must remain constant throughout the entire trial. In the event the patient is re-consented and re-screened the patient must be given a new screening number. Screening numbers and patient identification numbers, once assigned, will not be re-used.

4.2 Enrollment

Patients will be enrolled into the treatment phase of the study after all Screening (Group3) and qualification assessments have been completed and after the Investigator has verified that they are eligible per criteria in Sections 5.1 and 5.2. No patient may begin treatment prior to enrollment.

Eligible patients will be enrolled using an Interactive Voice/Web-Response System (IXRS).

5. PATIENT ELIGIBILITY

To be eligible to participate in this study candidates must meet the following eligibility criteria within 2 weeks of Study Day 1, or at the time point specified in the individual eligibility criterion listed.

5.1 Inclusion Criteria

1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law
2. Age ≥ 18 years at time of informed consent
3. Groups 1 and 2: Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement.

   Groups 2 and 3: Patients must also meet the following criteria in order to enter into the open-label Study:

   a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L)

   b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) supported by documentation of at least 1 of the following:

      - Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1)
      - Post heparin plasma LPL activity of ≤ 20% of normal in medical history. Note: testing of LPL activity should not be performed to confirm eligibility for the study

   c. Group 2: Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 index study

      Group 3: Fasting TG ≥ 750 mg/dL at Screening for this open-label study
4. Able and willing to participate in a 65-week study

5. Satisfy 1 of the following:

   a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved), abstinent*, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration.

   b. Males: Surgically sterile, abstinent* or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration.

   * Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception

5.2 Exclusion Criteria for Group 1 (ISIS 304801-CS6) and Group 2 (ISIS 304801-CS16) Index Study Roll-over Patients

1. Have any new condition or worsening of existing condition which in the opinion of the Investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study.
2. Unwilling to comply with lifestyle requirements for the duration of the study (Section 6.3).

Exclusion Criteria for Group 3 (patients who did not participate in an index study)

1. Diabetes mellitus with any of the following:
   a. Newly diagnosed within 12 weeks of screening
   b. HbA1c ≥ 9.0% at Screening
   c. Recent change in anti-diabetic pharmacotherapy (change in dosage or addition of new medication within 12 weeks of screening [with the exception of ± 10 units of insulin])
   d. Anticipated need to change dose or type of medication during the treatment period of the Study (with the exception of ± 10 units of insulin)
   e. Current use of GLP-1 agonists
2. Severe hypertriglyceridemia other than due to familial chylomicronemia syndrome
3. Active pancreatitis within 4 weeks prior to screening

4. History within 6 months of screening of acute or unstable cardiac ischemia (myocardial infarction, acute coronary syndrome, new onset angina), stroke, transient ischemic attack or unstable congestive cardiac failure requiring a change in medication or major surgery within 3 months of screening
5. Any of the following laboratory values at Screening
    a. Hepatic:
        - Total bilirubin > upper limit of normal (ULN), unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL
        - ALT > 2.0 x ULN
        - AST > 2.0 x ULN
    b. Renal:
        - Persistently positive (2 out of 3 consecutive tests ≥ 1+) for protein on urine dipstick. In the event of a positive test eligibility may be confirmed by a quantitative total urine protein measurement of < 500 mg/24 hrs
        - Persistently positive (2 out of 3 consecutive tests ≥ trace positive) for blood on urine dipstick. In the event of a positive test eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field
        - Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault < 50 mL/min (MDRD or CKD-EPI formulas can be used instead of Cockcroft-Gault for estimation of GFR in patients with low body weight after discussion with Sponsor Medical Monitor)
    c. Platelet count < lower limit of normal (LLN) for the central laboratory (i.e., < 140,000/mm^3)
    d. Cardiac Troponin I > ULN at Screening
    e. LDL-C > 130 mg/dL at Screening
    f. Any other laboratory abnormalities which, in the opinion of the Investigator or the Sponsor, would make the patient unsuitable for inclusion
6. Uncontrolled hypertension (BP > 160/100 mm Hg)
7. History of bleeding diathesis or coagulopathy or clinically-significant abnormality in coagulation parameters at Screening
8. History of heart failure with NYHA greater than Class II
9. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1

10. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B
11. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated
12. Treatment with another investigational drug, biological agent, or device within 1-month of screening, or 5 half-lives of investigational agent, whichever is longer
13. Unwilling to comply with lifestyle requirements (Section 6.3)
14. Use of any of the following:
    a. Statins, omega-3 fatty acids (prescription and OTC), or fibrates unless on a stable dose for at least 3 months prior to screening and dose and regimen expected to remain constant during the treatment period. Patients taking OTC omega-3 fatty acids should make every effort to remain on the same brand throughout the study
    b. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to screening
    c. Systemic corticosteroids or anabolic steroids within 6 weeks prior to screening unless approved by the Sponsor Medical Monitor
    d. Atypical antipsychotic medications (e.g., olanzapine and clozapine) unless on a stable dose for at least 3 months prior to screening and dose and regimen expected to remain stable throughout the study
    e. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to screening and dose and regimen expected to remain constant during the treatment period
    f. Glybera gene therapy within 2 years prior to screening
    g. Oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, and apixaban) unless on a stable dose for at least 4 weeks prior to screening and regular clinical monitoring is performed
    h. Tamoxifen, estrogens or progestins unless on a stable dose for at least 4 months prior to screening and dose and regimen expected to remain constant during the treatment period
    i. Plasma apheresis within 4 weeks prior to screening or planned during the study
    j. Prior exposure to ISIS 304801
    k. Any other medication unless stable at least 4 weeks prior to screening (Occasional or intermittent use of over-the-counter medications will be allowed at Investigator's discretion)
15. Blood donation of 50 to 499 mL within 30 days of screening or of > 499 mL within 60 days of screening

16. Known hypersensitivity to any of the excipients of the Study Drug (ISIS 304801 or placebo)
17. Have any other conditions, which, in the opinion of the Investigator or the Sponsor would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the study

6. STUDY PROCEDURES

6.1 Study Schedule

All required study procedures are outlined in Appendices A, B, C, and D.

6.1.1 Qualification (Groups 1 and 2)

Please refer to Section 4.1 and Appendix A.

6.1.2 Screening and Qualification (Group 3)

Before any study-specific procedures or evaluations are initiated, patients must sign and date the informed consent form. An 8-week period, including a diet stabilization period of at least 6 weeks (screening and diet stabilization period may be reduced, per Sponsor approval, if the patient is following a diet for optimal control of TGs and disease management prior to screening) is given to perform the screening evaluations. The qualification assessments will be performed at Week -2 to -1, ideally after patient eligibility has been determined, and on Study Day 1. Abnormal screening results may be retested for review by the Study Medical Monitor for eligibility purposes

6.1.3 Treatment Period

The patients, Investigators, study staff, and the Sponsor will remain blinded to lipid data through the last patient's Week 13 visit of the open-label study or until results from the database locks for the ISIS 304801-CS6 and ISIS 304801-CS16 index studies become available, whichever comes first.

During the treatment period, patients will report to the study center for clinic visits a minimum of 5 times during Weeks 1-52 (see Schedule of Procedures in Appendix A). Study Drug will be administered once weekly unless the patient is on a biweekly dosing schedule for safety reasons (Section 8.1). Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), AEs, concomitant medication/procedure information, lipid panel, blood viscosity, volanesorsen plasma concentrations, immunogenicity (IM) testing, platelet aggregation, liver/spleen MRI, ECGs, echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Adverse events at the injection site should be collected as adverse events. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period and all patients will complete a daily food diary for one week prior to their quarterly visit. All blood and urine samples should be collected prior to volanesorsen administration. Blood sampling at Weeks 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, and 51 may be conducted by a home healthcare nurse. Approval for study procedures to be conducted

by a home healthcare nurse on other outpatient visit days will require prior approval by the Sponsor. Patients must be fasted prior to drawing all blood samples and samples drawn locally should also be sent to the central laboratory for analysis whenever possible. Dosing instructions and training will be provided to the patient where applicable.

All reasonable attempts should be made to ensure compliance with the visit schedule as outlined in Appendix A. However, in the event that a visit does not occur or is delayed, all subsequent visits should be calculated based on the time elapsed since Day 1 rather than from the date of the previous visit.

6.1.4 Extended Treatment Period

Patients will have the option of continuing dosing for up to an additional 52 weeks until an expanded access program is approved and available in their country.

During the extended treatment period, patients will report to the study center for clinic visits during Weeks 54-104 (see Schedule of Procedures in Appendix A). Study Drug will be administered once weekly unless the patient is on a biweekly dosing schedule for safety reasons (Section 8.1). Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), AEs, concomitant medication/procedure information, lipid panel, volanesorsen plasma concentrations, IM testing, ECGs, and physical examinations will be performed according to the Schedule of Procedures in Appendix A. Adverse events at the injection site should be collected as adverse events. Dietary counseling will be reinforced at intervals throughout the extended treatment period. All blood and urine samples should be collected prior to volanesorsen administration. Blood sampling at Weeks 53, 54, 55, 56, 57, 58, 59, 60, 61, 62,63, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, and 103 may be conducted by a home healthcare nurse. Approval for study procedures to be conducted by a home healthcare nurse on other outpatient visit days will require prior approval by the Sponsor. Patients must be fasted prior to drawing all blood samples and samples drawn locally should also be sent to the central laboratory for analysis whenever possible. Dosing instructions and training will be provided to the patient where applicable.

6.1.5 Pharmacokinetic (PK) Subgroup

A subgroup of patients will participate in an extended PK collection. Patients in this subgroup will have more frequent PK sampling over a 24-hour period following the first dose on Study Day 1 in order to evaluate the plasma PK parameters of volanesorsen. Patients in this subgroup will have an additional visit to the clinic, or by a home healthcare nurse, on Day 2 to collect a 24-hour post-dose blood draw after dosing on Day 1. The detailed PK sampling schedules are outlined in Appendix C.

Participation in the PK subgroup is optional for sites and patients, and consent may be withdrawn for the subgroup-specific procedures (e.g., multiple blood draws for PK) without being withdrawn from the study. If a patient withdraws consent from the subgroup procedures, he/she should remain on study and continue to follow all the non-subgroup assessments and procedures as outlined in Appendix A.

6.1.6 Post-Treatment Period

After completion of the Week 52 visit assessments, patients will have the option of participating in an expanded access program or continuing dosing for up to an additional 52 weeks until an expanded access program is approved and available in their country as described in Section 6.1.4. Patients not participating in an expanded access program will enter the 13-week post-treatment evaluation period. This 13-week post-treatment evaluation period consists of 7 Study Center visits on Weeks 53, 54, 55, 56, 57, and 58 (which may be conducted by a home healthcare nurse), and Week 65 as outlined in the Schedule of Procedures in Appendix A. Patients who complete, or terminate early from, the extended treatment period without subsequently participating in an expanded access program will enter a 13-week post-treatment evaluation period consisting of 7 Study Center visits on Weeks 105, 106, 107, 108, 109, and 110 (which may be conducted by a home healthcare nurse), and Week 117 as outlined in the Schedule of Procedures in Appendix A.

6.2 Additional Study Assessments

6.2.1 Laboratory Assessments

Laboratory analyte samples will be collected throughout the study. A list of these analytes is contained in Appendix B.

Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1-week and the result must be reviewed by the Investigator and confirmed to be acceptable before dosing can continue. All platelet count results will be promptly reviewed by the Investigator to determine if the count has met a stopping rule, or the dose reduction rule of 100,000/mm^3, or the dose pause rule of 75,000/mm^3.

Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor.

6.2.2 Physical Exams and Vital Signs

Physical exams and vital signs will be performed as indicated in the Schedule of Procedures (Appendix A). Vital signs should include weight, blood pressure, pulse rate, respiratory rate and body temperature. Blood pressure and pulse rate will be recorded after the patient has been in a sitting position for at least 5 minutes. Semi-supine systolic and diastolic blood pressure should always be measured on the same arm (preferentially on the left arm). Height will be measured at the Day 1 visit.

6.2.2.1 Eruptive Xanthoma

At each visit, patients will be asked whether they have had any episodes of eruptive xanthoma since their last visit and the number/duration of the events will be recorded. Physical exams should also include skin examination for presence/resolution of eruptive xanthomas. If a patient experiences an episode of eruptive xanthoma during the study, photos of the area should be taken, if possible.

6.2.2.2 Lipemia Retinalis

If possible, lipemia retinalis will be assessed by fundus photography prior to administration of the first dose of Study Drug (for ISIS 304801-CS16 roll-over patients) and repeated at Week 52. Images will be evaluated by an independent assessor, blinded to the patient's treatment assignment.

6.2.3 Echocardiography

Echocardiography for assessment of left and right ventricular function and mitral and aortic valve function will be conducted at Week 26 and Week 52 in all patients. For the purpose of assessment of treatment-emergent changes, all echocardiograms will be evaluated on an ongoing basis by an independent central reader. Results will be provided to the DSMB for their review.

6.2.4 ECG

The ECG will be recorded after the patient has been resting in a supine position for at least 5 minutes. ECGs will be performed in triplicate at Week 13, Week 26, Week 38, Week 52, and Week 65. Patients in the Extended Treatment Period will have ECGs performed in triplicate at Week 76 and Week 104.

6.2.5 MRI

MRI of the liver and spleen will be conducted at Week 52 for all patients for whom MRI is not contraindicated, e.g., patients having metal implants.

MRIs will be conducted using standardized procedures and settings. MRIs will be read by an independent central reader to assess liver fat and liver and spleen size**.**

6.2.6 Quality of Life Assessments

All patients will complete Quality of Life Questionnaires (EQ-5D and SF-36) at Week 1, Week 13, Week 26, Week 52, and Week 65.

6.2.7 Disease Symptom Diary

All patients will complete a symptom questionnaire once a week starting at the beginning of the qualification period and continuing to the end of the post-treatment follow-up period (Week 65).

6.2.8 Diet Monitoring

The diets of patients enrolled in the study will be monitored as follows:

1. All patients will be required to maintain a 7-day food diary prior to Week 1, Week 13, Week 26, Week 52, and Week 65.

2. Patients will receive diet/alcohol counseling by qualified study personnel at clinic visits throughout the course of the study. Qualified study personnel will telephone the patient to provide diet/alcohol counseling for visits that are conducted by a clinical service. Patients in the Extended Treatment Period will receive diet/alcohol counseling by qualified study personnel at clinic visits only.

3. In addition to the 7-day food diary and the diet /alcohol counseling during clinic visits, telephone calls from a dietitian or qualified study personnel to assess as to how each patient is maintaining their diet may be conducted randomly during the treatment and post treatment follow-up periods.

6.2.9 Family History

Family history of hypertriglyceridemia and pancreatitis will be collected for each patient.

6.2.10 Chart Review for Incidents of Acute Pancreatitis in Medical History (Group 2 and 3)

Patient records will be reviewed for incidents of acute pancreatitis occurring up to 5 years prior to screening and information relating to these events will be collected for independent adjudication.

6.3 Restriction on the Lifestyle of Patients

6.3.1 Contraception Requirements

All male patients and women of childbearing potential must refrain from sperm/egg donation and either be abstinent[†] or, if engaged in sexual relations of child-bearing potential, practice effective contraception from the time of signing the informed consent form until at least 13 weeks after their last dose of study treatment.

Male patients must also encourage their female partner to use effective contraception from the time of signing the informed consent until 13 weeks after the subject's last dose of study treatment.

For the purposes of this Study, women of childbearing potential are defined as any female who has experienced menarche, and who does not meet 1 of the following conditions:

- Postmenopausal: 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved
- 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Post hysterectomy

For the purposes of the study, effective contraception is defined as follows:

For male patients:

- Effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the use of condoms together with spermicidal foam/gel/film/ cream/suppository. Male patients must also encourage their female partner to use effective contraception from the time of signing the informed consent until 3 months after the patient's last dose of study treatment. Effective contraceptive for the female partner includes: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or barrier methods (female condom[*], diaphragm, sponge, cervical cap) together with spermicidal foam/gel/film/cream/suppository. Male

patients with partners that are pregnant must use condoms to ensure that the fetus is not exposed to the Study Drug.

For female patients:

- Using 1 or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or any 2 barrier methods (a combination of male or female condom* with diaphragm, sponge, or cervical cap) together with spermicidal foam/gel/film/cream/suppository.

* Note: A female condom and a male condom should not be used together as friction between the two can result in either product failing.

† Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception

6.3.2 Other Requirements

All patients will be required to fast for at least 10 hours and preferably not more than 12 hours before visits requiring fasted blood sampling.

All patients will be encouraged to follow a diet comprising ≤ 20 g fat per day during the study.

Alcohol should not be consumed during the study.

All patients will be given an instruction card that must be presented to the treating physician if a suspected case of pancreatitis occurs. The card will explain that the patient is in a clinical trial and that serum lipase and/or amylase measures should be done in order to adjudicate the event, based on Atlanta Classification (Banks et al. 2013). If serum or amylase activity is less than 3 x upper limit of normal (ULN), imaging, preferably contrast-enhanced computed tomography, should be considered to confirm the diagnosis of acute pancreatitis per the Atlanta Criteria.

7. STUDY DRUG

7.1 Volanesorsen Description

Volanesorsen drug product (ISIS 304801) characteristics are listed in Table 1.

Volanesorsen (ISIS 304801) is contained in glass prefilled syringes (PFS). Volanesorsen and its storage and preparation instructions will be provided by the Sponsor or designee. Volanesorsen must be stored securely at 2 to 8 °C and be protected from light.

Table 1 Volanesorsen (ISIS 304801) Characteristics

Strength	200 mg/mL
Volume/Formulation	1.5 mL solution per PFS
Dose	300 mg once weekly
Route of Administration	SC

7.2 Packaging and Labeling

The Sponsor will provide the Investigator with packaged volanesorsen labeled (ISIS 304801) in accordance with specific country regulatory requirements.

7.3 Study Drug Accountability

The study staff is required to document the receipt, dispensing, and return/destruction of volanesorsen provided by the Sponsor. The Study Center must return all unused volanesorsen to the Sponsor or designee. All used syringes must be disposed of as per the site's hazardous waste destruction policy.

8. TREATMENT OF PATIENTS

8.1 Volanesorsen Administration

For each individual patient, volanesorsen will be administered subcutaneously as a single 1.5 mL 300 mg injection once weekly for Weeks 1-52. Patients entering this ISIS 304801-CS7 study on a reduced dose or dose frequency of Study Drug (volanesorsen), for safety or tolerability reasons in their index study (ISIS 304801-CS6 or ISIS 304801-CS16), will receive a reduced dose or dose frequency of volanesorsen for continued safety or tolerability as outlined in Sections 8.5 and 8.6. Patients entering this CS7 study having dose or dose frequency reduced in the CS16 index study after 13 weeks of treatment, as outlined in CS16 Amendment 4 Section 8.7, can receive the 300 mg once weekly dose of volanesorsen.

Patients should receive 1 dose per week, with weeks always defined relative to Study Day 1. For example if a patient receives the first dose on a Monday, subsequent doses should be given on Mondays, if possible. If a patient misses an injection, or if dosing on the usual day is not possible, the patient can reschedule the injection provided that 2 doses are administered at least 2 days apart.

Please refer to the Study Drug Manual provided by the Sponsor for more detailed instructions for volanesorsen preparation and administration.

8.2 Other Protocol-Required Drugs

There are no other protocol-required drugs.

8.3 Other Protocol-Required Treatment Procedures

There are no other protocol required treatment procedures for this study.

8.4 Treatment Precautions

There are no specific treatment precautions required for this study.

8.5 Safety Monitoring Rules

Please refer also to the 'Guidance for Investigator' section of the Investigator's Brochure.

For the purposes of safety monitoring baseline is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 (e.g., qualification assessments or

assessments from the final visits of ISIS 304801-CS6 and ISIS 304801-CS16 index studies if used for qualification).

In addition to the standard monitoring of clinical safety parameters, the following guidelines are provided for the monitoring of selected parameters chosen based on preclinical and clinical observations.

Confirmation Guidance: At any time during the study (Treatment or Post-Treatment Periods), the initial clinical laboratory results meeting the safety monitoring or stopping criteria presented below **must be confirmed** by performing measurements (ideally in the same laboratory that performed the initial measurement) on new specimens. All new specimen collections should take place as soon as possible (ideally within 3 days of the initial collection). For stopping rules, if the initial laboratory result is observed during the Treatment Period, the results from the retest **must be available** prior to administering the next dose of volanesorsen.

In addition to the safety monitoring parameters listed below, the Sponsor may request confirmation of additional lab values.

Re-dosing Guidance: Patients with initial laboratory test values that reach a stopping rule must not be re-dosed until the re-test results are available. In general, patients who do not meet the stopping rules based upon retest may continue dosing. However, the Investigator and the Sponsor Medical Monitor (or appropriately qualified designee) should confer as to whether additional close monitoring of the patient is appropriate. Reduction in dose or dose frequency may also be initiated as noted in Section 8.7. If any of the stopping criteria described below (refer to Sections 8.6.1 to 8.6.3) are met, the patient will be dose paused or permanently discontinued (as described in the stopping criterion concerned) from further treatment with volanesorsen, and evaluated fully as outlined below and in consultation with the Sponsor Medical Monitor or appropriately qualified designee, and will be followed up in accordance with Section 8.8 of the protocol.

8.5.1 Safety Monitoring for Liver Chemistry Tests

The following rules are adapted from the draft guidance for industry, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," issued by the U.S. Department of Health and Human Services, Food and Drug Administration, July 2009. For a definition of Baseline please refer to guidance in Section 8.5 above.

In the event of an ALT or AST measurement that is > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) at any time during the study (Treatment or Post-Treatment Period), the initial measurement(s) should be confirmed as described above. Additional confirmatory measurements should also be performed if ALT or AST levels increase to 5 x ULN.

Frequency of Repeat Measurements: Patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) should have their liver chemistry tests (ALT, AST, alkaline phosphatase (ALP), international normalized ratio (INR) and total bilirubin) retested at least once-weekly until ALT and AST levels become ≤ 1.2 x ULN or 1.2 x baseline value if the baseline value was > ULN.

Further Investigation into Liver Chemistry Elevations: For patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), the following evaluations should be performed:

1. Obtain a more detailed history of symptoms and prior and concurrent diseases
2. Obtain further history for concomitant drug use (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
3. Obtain a history for exposure to environmental chemical agents and travel
4. Serology for viral hepatitis (HAV IgM, HBsAg, HCV antibody, CMV IgM, and EBV antibody panel)
5. Serology for autoimmune hepatitis (e.g., antinuclear antibody [ANA])

Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic CT or MRI scans, may be performed at the discretion of the Investigator, in consultation with the Sponsor Medical Monitor. Repetition of the above evaluations should be considered if a patient's ALT and/or AST levels reach 5 x ULN.

8.5.2 Safety Monitoring for Platelet Count Results

Actions to be taken in the event of reduced platelet count are shown in Table 3 in Section 8.6.3.

Monitor every 1 week unless otherwise specified.

Study Drug administration is contingent on the availability of the immediately preceding test result. An interpretable platelet value must be available within 7 days prior to dosing. Only the study doctor or qualified designee can authorize continued Study Drug administration based on an acceptable platelet value. Patients should not administer a dose until they have been contacted by their study doctor or designee and told that it is acceptable to dose. Authorization to dose must be documented in the patient's medical records.

Due to the 1 to 2-year study duration it is anticipated that patients may undertake travel including vacations, which may impede weekly platelet monitoring. In some situations, it may be possible to arrange for local laboratory testing or use of the home healthcare service at their temporary location. The intent is to maintain weekly platelet monitoring and dosing where possible, as well as Investigator site contact with the study patients. However, if the above options are not possible, a temporary interruption of study treatment will be planned with a prompt blood draw upon the patient's return which must be reported and reviewed by the Investigator prior to the patient resuming dosing.

The tests outlined in Table 2 should also be performed as soon as possible. Additional lab tests will be determined by the Sponsor Medical Monitor or designee in consultation with the Investigator.

Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor (See also Stopping Rules Section 8.6.3).

Table 2 Labs to Be Performed in the Event of a Platelet Count Less than the Lower Limit of Normal (x2) or < 100,000/mm^3 (x1)*

*In patients who have any 2 occurrences (consecutive or non-consecutive) of platelet count less than the lower limit of normal or who have any 1 occurrence of platelets < 100,000/mm^3. Labs only need to be performed once. Labs may be collected over multiple visits, if blood requirements are a concern, as per Investigator discretion.

Note: The following labs may change as additional data is assessed, and sites will be updated regarding any changes.

To Be Performed at Local Lab
Peripheral smear (should be performed locally, fixed and sent to central lab for review)
Fibrinogen split products or D-dimer on fresh blood
To Be Performed at Central Lab
Citrated sample for platelets
Coagulation panel (PT/INR, aPTT)
CBC with reticulocytes
Folate (folic acid)
Vitamin B12
Fibrinogen
von Willebrand factor
Total globulins, total IgA, IgG and IgM
Complement: total C3, total C4, Bb, C5a
hsCRP
Helicobacter pylori (breath test)
Serology for:
HBV, HCV, HIV (if not done recently for screening)
Rubella
CMV
EBV
Parvo B19
Auto-antibody screen:
Antiphospholipid
Rheumatoid factor
Anti-dsDNA
Anti-thyroid
To Be Performed at Specialty Lab(s)
Antiplatelet antibodies and Anti-PF4 assay
Anti-ASO antibody

8.5.3 Safety Monitoring for Minor Bleeding Events

Minor bleeding events are those that do not fulfill the criteria for major bleeding or clinically-relevant, non-major bleeding events (which are defined in Section 8.6.3), for example excess bruising, petechiae, gingival bleeding on brushing teeth. If a minor bleeding event occurs, the Investigator must notify the Sponsor Medical Monitor and additional testing of coagulation parameters activated partial thromboplastin time (aPTT), prothrombin time (PT), INR and platelet count should be performed.

8.5.4 Safety Monitoring for Constitutional Symptoms

Patients will be instructed to promptly report any signs of symptoms of fever or constitutional symptoms that may arise during the study and the Investigator should closely evaluate all potential causes, including concomitant illness. Patients that experience persistent constitutional symptoms should be discussed with the Sponsor Medical Monitor or designee to determine whether additional monitoring or laboratory tests are required.

8.5.5 Safety Monitoring for LDL-C Elevations

Beginning at Week 13, laboratory alerts will be in place to notify the Investigator if a patient has a low-density lipoprotein-cholesterol (LDL-C) > 160 mg/dL (> 130 mg/dL for patients with T2DM) on 2 consecutive visits. If this occurs, LDL-C values for this patient will be unblinded for the remainder of the study and the Investigator will be encouraged to initiate/adjust treatment to lower LDL-C according to country-specific guidelines (e.g., initiate statin therapy or increase the statin dose for patients who are already on treatment).

8.5.6 Safety Monitoring for Insulin, Oral Antidiabetic Medication and Glucose

All patients on insulin will monitor their glucose levels with a glucometer as per standard practice guidelines and bring their glucometer or glucometer log printout to every clinic visit. In addition, patients who are not on insulin but use a glucometer should also bring their glucometer and/or glucometer log printout to every clinic visit.

- The Investigator or delegate will review the glucometer reading or printout at every clinic visit to evaluate if fasting pre-breakfast self-monitored plasma glucose values exceed threshold values as per the Safety Monitoring Rules for Hyperglycemia below.

All diabetic patients will note any changes in their insulin dose and /or oral antidiabetic therapy, as well as any hypoglycemic episode they may experience.

- The Investigator or delegate will ask patients at every clinic visit if they made changes in their insulin dose or oral antidiabetic therapy, and if they experienced a hypoglycemic episode.
    - Patients will be instructed on the monitoring and management of hypoglycemic episodes at each visit.
    - Documented symptomatic hypoglycemic episodes should be captured as adverse events in the adverse event CRF. Documented symptomatic hypoglycemia is defined as typical hypoglycemia symptoms accompanied by measured plasma glucose ≤ 70 mg/dL (≤ 3.9 mmol/L).

- Any changes in insulin dose or oral antidiabetic therapy should be captured into the Concomitant Medication CRF.

8.5.7 Safety Monitoring for Documented Severe Hypoglycemia

A **documented severe hypoglycemic event** is defined as 1 in which the patient requires assistance of another person to obtain treatment for the event and has a plasma glucose level ≤ 70 mg/dL (≤ 3.9 mmol/L). The rescue treatment of hypoglycemia may include IV glucose or buccal or intramuscular glucagon.

The definition of severe symptomatic hypoglycemia includes all episodes in which neurological impairment was severe enough to prevent self-treatment and which were thus thought to place patients at risk for injury to themselves or others. Note that "requires assistance" means that the patient could not help himself or herself. Someone being kind that assists spontaneously the patient when not necessary does not qualify as "requires assistance."

Severe hypoglycemia will be qualified as a SAE only if it fulfills SAE criteria.

If a patient presents with symptoms of hypoglycemia, the Investigator will need to take immediate action to confirm the patient's glucose level and treat the patient accordingly.

The experience of hypoglycemia may vary greatly from patient to patient. However, there are certain classical signs and symptoms, of which patients should be aware as a clue that their blood glucose may be low. Common symptoms include headache, heart pounding, confusion, disorientation, numbness or tingling, pale skin, shakiness or tremulousness, increased appetite, anxiousness or nervousness, lightheadedness or dizziness, sweating, and weakness. Coma could occur if blood sugar correction is not performed.

If patients suspect they might be having a hypoglycemia reaction, they should check their blood glucose using their meters as soon as possible, before treatment if possible, provided they feel it is safe to do so. If there is doubt about safety they should treat the event first, using some sugar, milk, or juice for example, then obtain and record a blood glucose value as soon as possible thereafter. The time and nature of treatment should be noted, and especially if any blood glucose result was before or after treatment. It would be helpful for the patient to note if a contributory factor (e.g., missed or reduced meals, unaccustomed physical activity) occurred earlier in the day of the event.

8.5.8 Safety Monitoring for Hyperglycemia

Upward dose titration and/or addition of any other anti-hyperglycemic agent(s) will not be allowed during the course of the study, unless specific threshold values are met at Week 13 or later and confirmed on subsequent testing (ideally within 1-week of the initial test).

HbA1c is monitored every 3 months throughout the study. In addition, patients on insulin should self-monitor their plasma glucose (SMPG) routinely on a glucometer as per practice guidelines. If a fasting pre-breakfast SMPG value exceeds the specific glycemic limit, the patient should check it again on the following 2 days. If all the fasting pre-breakfast values on 3 consecutive days exceed the specific limit, the patient should contact the Investigator and an unscheduled central laboratory FPG measurement and HbA1c should be performed.

The threshold values are defined as:

- FPG > 270 mg/dL (15.0 mmol/L)
- HbA1c > 9% (for patients with baseline HbA1c < 8% and HbA1c increase of more than 1% from baseline (for patients with baseline HbA1c ≥ 8 and < 9%)

In case of confirmed FPG/HbA1c above the threshold value, the Investigator should ensure that no reasonable explanation exists for insufficient glucose control and in particular that:

- Plasma glucose was actually measured in the fasting condition (i.e., after at least 10 hours fast)
- Absence of intercurrent disease which may jeopardize glycemic control. In case of an emergency (e.g., surgery, infection), the Investigator can take appropriate measures for glycemic control
- Compliance to treatment is appropriate
- Compliance to diet and lifestyle is appropriate

If any of the above can reasonably explain the insufficient glycemic control, the Investigator should consider the following:

- Investigation and treatment of intercurrent disease (to be reported in adverse event (AE)/concomitant medication parts of the e-CRF)
- Stress on the absolute need to be compliant to treatment
- Organize a specific interview with a Registered Dietician or other qualified nutrition professional and stress on the absolute need to be compliant to diet and lifestyle recommendations

A FPG/HbA1c follow-up assessment should be arranged after appropriate action has been taken. If none from the above-mentioned reasons can be found, or if appropriate action fails to decrease FPG/HbA1c under the threshold values, additional medication may be introduced at the Investigator's discretion and according to local guidelines after discussion with the Sponsor Medical Monitor.

8.5.9 Acute Pancreatitis

If a patient has an episode of acute pancreatitis, dosing with Study Drug should be suspended temporarily until the patient is clinically stable. The suitability of the patient for continued dosing and the need for any modification to treatment schedule (refer to Section 8.7) will be determined by the Investigator in consultation with the Study Medical Monitor.

8.6 Stopping Rules

For the purposes of stopping rules baseline is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1.

8.6.1 Stopping Rules for Liver Chemistry Elevations

In the event of laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor,** dosing of a patient with volanesorsen will be stopped permanently; values that are not confirmed due to failure to retest or missing lab values will be presumed confirmed:

1. ALT or AST > 8 x ULN, which is confirmed
2. ALT or AST > 5 x ULN, which is confirmed and persists for ≥ 2 weeks
3. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed **and** total bilirubin > 2 x ULN or INR > 1.5
4. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed, and the new appearance (i.e., onset coincides with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> ULN) felt by the Investigator to be potentially related to hepatic inflammation

8.6.2 Stopping Rules for Renal Function Test Results

In the event of a persistent elevation that is observed over 2 consecutive weeks, for any of the 3 criteria below, dosing of a patient with volanesorsen may be stopped temporarily:

1. Serum creatinine increase that fulfill all of the following criteria: ≥ 0.3 mg/dL (26.5 µmol/L) and ≥ 40% above baseline creatinine values and > ULN
2. Proteinuria, dipstick 2 + (confirmed by dipstick retest and then further confirmed by a quantitative total urine protein measurement of > 1.0 g/24-hour)
3. Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault ≤ 40 mL/min that is confirmed by a 24-hour urine collection

The possible dosing re-initiation or follow-up schedule for any events meeting either of these criteria will be determined by the Investigator **in consultation with** the Sponsor Medical Monitor or designee.

8.6.3 Stopping Rules for Platelet Count Results

Actions to be taken in the event of a low platelet count are summarized in Table 3 below.

In the event of a platelet count less than 75,000/mm^3 that is associated with major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with volanesorsen will be stopped permanently. The follow-up schedule for any events meeting this stopping criterion will be determined by the Investigator in consultation with the Sponsor Medical Monitor.

In the event of any platelet count less than 50,000/mm^3, or a platelet count less than 75,000/mm^3 that occurs while the patient is on dosing at 300 mg every 2 weeks then dosing of a patient with volanesorsen will be stopped permanently. Platelet count will be monitored as outlined in Table 3.

Administration of steroids is recommended for patients whose platelet count is less than 50,000/mm^3. Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (**note:** may require continuation with oral steroids after methylprednisolone). Triglyceride levels will be monitored weekly, and AE monitoring will continue, during cortiscosteroid treatment and the laboratory alert will be changed from an increase of 2,000 to 500 mg/dL during that period.

In the event of a platelet count less than 75,000/mm^3, and in the absence of major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with volanesorsen should be suspended temporarily until the platelet count has recovered to> 100,000/mm^3. If dosing is continued it should be at a reduced dose frequency of 300 mg every 2 weeks (refer to Section 8.7). The suitability of the patient for continued dosing will be determined by the Investigator in consultation with the Study Medical Monitor and will be based on factors such as the original rate of decline in the patient's platelet count, whether any bleeding events were experienced by the patient, and the speed of recovery of platelet count upon holding of dosing.

If after the first dosing rechallenge the platelet count again falls below 75,000/mm^3, then dosing of the patient with Study Drug will be stopped permanently.

Definition of Major Bleeding Events (Schulman et al. 2005):

- Fatal bleeding, and/or
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarterial or pericardial, or intramuscular with compartment syndrome, and/or
- Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more within 24 hours, or leading to transfusion of 2 or more units of whole or red cells

Definition of Clinically-Relevant, Non-Major Bleeding Events (Schulman et al. 2005):

1. Multiple-source bleeding
2. Spontaneous hematoma > 25 cm^2
3. Excessive wound hematoma (not injection site related)
4. Macroscopic hematuria (spontaneous or lasting > 24 hours if associated with an intervention)
5. Spontaneous rectal bleeding; epitasis, gingival bleeding, hemoptysis, hematemesis
6. Bleeding after venipuncture for > 5 minutes

Table 3 Actions in Patients with Low Platelet Count or Drop in Platelet Count

Platelet Count on Rx	Drug Dose	Monitoring
	Study Drug administration is contingent on the availability of the immediately preceding test result. An interpretable platelet value must be available within 7 days prior to dosing. Only the study doctor or qualified designee can authorize continued Study Drug administration based on an acceptable platelet value. Patients should not administer a dose until they have been contacted by their study doctor or designee and told that it is acceptable to dose. Authorization to dose must be documented in the patient's medical records.	**Monitor every 1 week unless otherwise specified** Obtain additional lab tests (Table 2) if 2 occurrences consecutive or non-consecutive) of platelet count 140K - > 100K/mm^3 or 1 occurrence of platelet count ≤ 100K/mm^3. Labs only need to be performed once. Labs may be collected over multiple visits, if blood requirements are a concern, as per Investigator discretion.
> 100K/mm^3	Weekly 300 mg Study Drug administration	
100K/mm^3 - >75K/mm^3	Permanently reduce dose frequency to 300 mg every 2 weeks	
75K/mm^3 - >50K/mm^3	• If occurs while on dose of 300 mg every 2 weeks then permanently discontinue Study Drug, otherwise dose pause • When platelet count returns to > 100K/mm^3 restart dosing at dose frequency of 300 mg every 2 weeks **only if approved by Sponsor Medical Monitor**	• Monitor every 2-3 days until 2 successive values are > 75K/mm^3 then monitor every 1 week • Consider discontinuation of antiplatelet agents/NSAIDS/ anticoagulant medication
≤ 50K/mm^3	Permanently discontinue Study Drug	• Monitor daily until 2 successive values show improvement then monitor every 2-3 days until 2 successive values are > 75K/mm^3 then monitor every 1 week • Patient should be evaluated by a hematologist to provide diagnostic and therapeutic management • Steroids recommended*. It is strongly recommended that, unless the patient has a medical contraindication to receiving glucocorticoids, the patient receives glucocorticoid therapy to reverse the platelet decline. • Monitor triglyceride levels weekly and continue AE monitoring during steroid therapy • Discontinue antiplatelet agents/ NSAIDS/ anticoagulant medication while platelet count is < 50K/mm^3 if possible

* Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or methylprednisolone 30 mg/kg/day for 7 days (**note**: may require continuation with oral steroids after methylprednisolone)

8.7 Adjustment of Dose Frequency

Dose adjustments for platelet count reduction must be made in accordance with Section 8.6.3 and Table 3 (above).

Other dose adjustments, including dose interruptions, and/or decreasing the dose or dose frequency will be allowed for safety and tolerability. Any proposed adjustment to treatment schedule must be discussed with, and approved by, the Study Medical Monitor prior to initiation. Up to 2 adjustments in the treatment schedule may be allowed.

Patients may be dose paused in response to AEs after consultation with Study Medical Monitor.

8.8 Discontinuation of Study Treatment

A patient must permanently discontinue study treatment for any of the following:

- The patient becomes pregnant. Report the pregnancy according to instructions in Section 9.5.4
- The patient withdraws consent
- The patient experiences an AE that necessitates permanent discontinuation of study treatment
- The patient develops laboratory test abnormalities that meet any of the stopping rules listed in Section 8.6

The reason for discontinuation of study treatment must be recorded in the CRF and source documentation.

8.8.1 Follow-up Visits for Early Termination from Treatment Period

Any patient who discontinues early from the Treatment Period should be followed as per the platelet monitoring rules shown in in Section 8.6.3 for the first 6 weeks after discontinuing Study Drug. Following this period, if the platelet count is stable (at least 3 consecutive values that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3), the next platelet count should be taken within at least 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug. Patients should also be strongly encouraged to attend applicable landmark visits at Weeks 12, 13, 25, 26, and 50, 52 (calculated based on the time elapsed since Day 1) to collect fasting lipid panels and conduct safety assessments in accordance with the Schedule of Procedures in Appendix A. Any patient who discontinues treatment after Week 44 should also be strongly encouraged to attend a final follow-up visit (Week 65 visit assessments) approximately 13 weeks after their last dose of Study Drug, in addition to the applicable landmark visits.

If the patient declines or is unable to participate in the above, an early termination (ET) visit (Week 52 visit assessments) should be performed at the time of withdrawal, at a minimum, and ideally within 2 weeks from the last dose of Study Drug.

8.8.2 Follow-up Visits for Early Termination from Post-Treatment Follow-up Period

The patient who requests to withdraw from the study during the Post-Treatment Follow-up Period should be encouraged to follow the platelet monitoring rules shown in Table 3 in

Section 8.6.3 for the first 6 weeks after discontinuing Study Drug. Following this period, if the platelet count is stable (at least 3 consecutive values that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3), the next platelet count should be taken within at least 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug. Patients should also be encouraged to undergo a final follow-up visit (Week 65 (or Week 117 if terminating from the Extended Treatment Follow-Up Period), see Appendix A) prior to leaving the study.

If a patient withdraws due to an AE at any time during the study, the Investigator should arrange for the patient to have appropriate follow-up until the AE has resolved or stabilized.

8.9 Withdrawal of Patients from the Study

Patients must be withdrawn from the study for any of the following:

- Withdrawal of consent
- The patient is unwilling or unable to comply with the protocol

Other reasons for withdrawal of patients from the study might include:

- At the discretion of the Investigator for medical reasons
- At the discretion of the Investigator or Sponsor for noncompliance
- Significant protocol deviation

All efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information, including the reason for withdrawal from study, must be recorded in the CRF.

Any patient who withdraws consent to participate in the study will be removed from further treatment and study observation immediately upon the date of request. These patients should be encouraged to complete the ET study procedures and observations at the time of withdrawal (see Section 8.8 and Appendix A).

For patients withdrawn for reasons other than withdrawal of consent every effort should be made to complete the early termination study procedures and observations at the time of withdrawal (see Section 8.8 and Appendix A).

8.10 Concomitant Therapy and Procedures

The use of concomitant therapies or procedures defined below must be recorded on the patient's CRF. AEs related to administration of these therapies or procedures must also be documented on the appropriate CRF.

8.10.1 Concomitant Therapy

A concomitant therapy is any non-protocol specified drug or substance (including over-the-counter medications, herbal medications and vitamin supplements) administered between signing informed consent and completion of the post-treatment follow-up period. All concomitant medications/treatments and significant non-drug therapies (including supplements and assistive devices) received by a patient, including changes in the patient's current medications, must be

recorded in the patient's source documents and CRF. Patients taking over the counter (OTC) omega-3 fatty acids should make every effort to remain on the same brand throughout the study.

Allowed Concomitant Therapy

Any medications deemed necessary by the Investigator are allowed except those listed in the disallowed concomitant therapy.

Disallowed Concomitant Therapy

No lipid lowering therapies (e.g., fibrates, niacin, fish oil or other products containing omega-3 fatty acids [including OTC preparations]), -glucagon-like peptide-1 (GLP-1) agonists, Glybera, or systemic corticosteroids may be started or adjusted after baseline qualification. Doses of existing oral anti-diabetic medication, oral contraceptives, hormone replacement therapy, anticoagulants, or drugs or dietary supplements with potential lipid-altering effects should not be adjusted. Study patients are prohibited from receiving other experimental agents during the study. This includes marketed agents at experimental dosages that are being tested for the treatment of hypertriglyceridemia.

Patients should consult with the Site Investigator or designee prior to initiating any new medication, including non-prescription or herbal compounds or any other non-drug therapy.

8.10.2 Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between signing of informed consent and Week 65 (or Week 117 if patient enters the extended treatment period) visit.

Disallowed Concomitant Procedure

Plasma apheresis is not allowed during the study.

8.11 Treatment Compliance

Compliance with treatment dosing is to be monitored and recorded by Study Center staff. The Study Center staff is required to document the receipt, dispensing, and return/destruction of volanesorsen. Patients that are self-administering volanesorsen at home must record treatment in a dosing diary that will be reviewed periodically by Study Center staff and the Clinical Monitor.

9. SERIOUS AND NON-SERIOUS ADVERSE EVENT REPORTING

9.1 Sponsor Review of Safety Information

Safety information will be collected, reviewed, and evaluated by the Sponsor in accordance with the Safety Management Plan throughout the conduct of the clinical trial.

9.2 Regulatory Requirements

The Sponsor is responsible for regulatory submissions and reporting to the Investigators of serious adverse events (SAEs) including suspected unexpected serious adverse reactions (SUSARs) per the International Conference on Harmonization (ICH) guidelines E2A and ICH

E6. Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines.

Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) will be notified of any SAE according to applicable regulations. The Independent DSMB will be notified of any SAE as specified in the DSMB charter.

In addition to the Investigator's assessment of relatedness, the Sponsor or designee will evaluate the available information and perform an independent assessment of relatedness. While the Sponsor may upgrade an Investigator's decision it is not permissible to downgrade the Investigator's opinion for the purposes of determining whether the SAE meets the definition of a SUSAR.

The following table identifies the SAEs that the Sponsor or designee will not report on an individual basis in an expedited manner because they are anticipated to occur in the study population independent of volanesorsen exposure. The Investigator still has the responsibility to report all SAEs to the Sponsor as described in Sections 9.4.1 to 9.4.3.5.

Table 4 Expected Event for the Protocol Defined Population by Preferred Term and the Expected Incidence

Preferred Term	Expected Incidence in the Protocol Defined Population (Gaudet et al. 2010 and 2013)
Pancreatitis associated events including the PTs of hereditary pancreatitis, pancreatitis, pancreatitis acute, pancreatitis chronic, pancreatitis necrotizing, pancreatitis relapsing	0.2-0.35 events per patient-year

Fatal pancreatitis associated events will be considered as unexpected and are reportable. The Sponsor and DSMB will monitor non-fatal pancreatitis associated SAEs using the incidence rate of the event compared to the rate expected in a non-volanesorsen exposed population. If the aggregate analysis indicates that an event is occurring significantly more frequently or at a greater severity than expected, then the event will be reported.

SAEs not specified in the table will be evaluated on case by case basis to determine whether there is a reasonable possibility that the drug caused the event. If the event is considered by the Sponsor or designee to meet the definition of a SUSAR the event will be reported.

9.3 Definitions

9.3.1 Adverse Event

An adverse event is any unfavorable and unintended sign (including a clinically-significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the study or use of investigational drug product, whether or not the AE is considered related to the investigational drug product.

9.3.2 Adverse Reaction and Suspected Adverse Reaction

An adverse reaction is any adverse event caused by volanesorsen.

A suspected adverse reaction is any adverse event for which there is a reasonable possibility that volanesorsen drug caused the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

9.3.3 Serious Adverse Event (SAE)

A serious adverse event is any adverse event that in the view of either the Investigator or Sponsor, meets any of the following criteria:

- Results in death
- Is life threatening: that is, poses an immediate risk of death at the time of the event

An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Hospitalization is defined as an admission of greater than 24 hours to a medical facility and does not always qualify as an AE
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly or birth defect in the offspring of the patient (whether the patient is male or female)
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

9.4 Monitoring and Recording Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the study (i.e., before informed consent) should be recorded as Medical History and not recorded as AEs unless the pre-existing condition worsened. The Investigator should always group signs and symptoms into a single term that constitutes a **single unifying diagnosis** if possible.

9.4.1 Serious Adverse Events

In the interest of patient safety, and in order to fulfill regulatory requirements, all SAEs (regardless of their relationship to volanesorsen) should be reported to the Sponsor or designee within 24 hours of the Study Center's first knowledge of the event. The collection of SAEs will

begin after the patient signs the informed consent form and stop at the end of the patient's follow-up period which is defined as the Week 65 visit (or Week 117 if patient enters the extended treatment period). When the Investigator is reporting by telephone, it is important to speak to someone in person versus leaving a message. An Initial Serious Adverse Event Form should be completed and a copy should be faxed to the Sponsor or designee.

Detailed information should be actively sought and included on Follow-Up Serious Adverse Event Forms as soon as additional information becomes available. All SAEs will be followed until resolution. SAEs that remain ongoing past the patient's last protocol-specified follow-up visit will be evaluated by the Investigator and Sponsor. If the Investigator and Sponsor agree the patient's condition is unlikely to resolve, the Investigator and Sponsor will determine the follow-up requirement.

9.4.2 Non-Serious Adverse Events

The recording of non-serious AEs will begin after the patient signs the informed consent form and will stop at the end of the patient's follow-up period, which is defined as the Week 65 visit (or Week 117 if patient enters the extended treatment period). The Investigator will monitor each patient closely and record all observed or volunteered AEs on the Adverse Event Case Report Form.

9.4.3 Evaluation of Adverse Events (Serious and Non-Serious)

The Investigator's opinion of the following should be documented on the Adverse Event Case Report Form:

9.4.3.1 Relationship to the Study Drug

The event's relationship to volanesorsen is characterized by 1 of the following:

- **Related:** There is clear evidence that the event is related to the use of volanesorsen, e.g., confirmation by positive rechallenge test
- **Possible:** The event cannot be explained by the patient's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and volanesorsen administration
- **Unlikely/Remote:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to volanesorsen administration and/or exposure suggests that a causal relationship is unlikely (For reporting purposes, Unlikely/Remote will be grouped together with Not Related)
- **Not Related:** The event can be readily explained by the patient's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and volanesorsen

9.4.3.2 Severity

The severity of AEs and SAEs will be graded based on criteria from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010 (refer to Appendix D). Any AE not listed in Appendix D will be graded as follows:

- **Mild:** The event is easily tolerated by the patient and does not affect the patient's usual daily activities
- **Moderate:** The event causes the patient more discomfort and interrupts the patient's usual daily activities
- **Severe:** The event is incapacitating and causes considerable interference with the patient's usual daily activities

If the event is an SAE, then all applicable seriousness criteria must be indicated (criteria listed in Section 9.3.3).

9.4.3.3 Action Taken with Volanesorsen

Action taken with volanesorsen due to the event is characterized by 1 of the following:

- **None:** No changes were made to volanesorsen administration and dose
- **Permanently Discontinued:** Volanesorsen was discontinued and not restarted
- **Temporarily Interrupted, restarted – same dose:** Dosing was temporarily interrupted or delayed due to the AE and restarted at the same dose
- **Reduced schedule:** Dosing frequency was reduced

9.4.3.4 Treatment Given for Adverse Event

Any treatment (e.g., medications or procedures) given for the AE should be recorded on the Adverse Event Case Report Form (treatment should also be recorded on the concomitant treatment or ancillary procedures CRF as appropriate).

9.4.3.5 Outcome of the Adverse Event

If the event is a non-serious AE then the event's outcome is characterized by 1 of the following:

- **AE Persists:** Patient terminates from the trial and the AE continues
- **Recovered:** Patient recovered completely from the AE
- **Became Serious:** The event became serious (the date that the event became serious should be recorded as the Resolution Date of that AE and the Onset Date of the corresponding SAE)
- **Change in Severity** (if applicable): AE severity changed

If the event is a SAE then the event's outcome is characterized by 1 of the following:

- **Ongoing:** SAE continuing
- **Persists (as non-serious AE):** Patient has not fully recovered but the event no longer meets serious criteria and should be captured as an AE on the non-serious AE eCRF (the SAE resolution date should be entered as the date of onset of that AE)
- **Recovered:** Patient recovered completely from the SAE (the date of recovery should be entered as the SAE resolution date)

- **Fatal:** Patient died (the date of death should be entered as the SAE resolution date)

9.4.4 Adjudication Committees

All SAEs that occur during the study that are consistent with a major acute cardiovascular event (MACE) will be adjudicated by a blinded, independent committee as outlined in the MACE Adjudication Charter.

All AEs and SAEs that occur during the study that are consistent with an event of acute pancreatitis will be adjudicated by a blinded, independent committee according to the Atlanta classification of acute pancreatitis (Banks et al. 2013) and as outlined in the Pancreatitis Adjudication Charter. In addition, data for prior episodes of acute pancreatitis or suspected pancreatitis will be collected by review of each patient's medical chart and these events will also be adjudicated.

9.5 Procedures for Handling Special Situations

9.5.1 Abnormalities of Laboratory Tests

Clinically-significant abnormal laboratory test results may, in the opinion of the Investigator, constitute or be associated with an AE. Examples of these include abnormal laboratory results that are associated with symptoms, or require treatment, e.g., bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac arrhythmias due to hyperkalemia. Whenever possible, the underlying diagnosis should be listed in preference to abnormal laboratory values as AEs. Clinically-significant abnormalities will be monitored by the Investigator until the parameter returns to its baseline value or until agreement is reached between the Investigator and Sponsor Medical Monitor. Laboratory abnormalities deemed not clinically-significant (NCS) by the Investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator should not be deemed NCS on the laboratory sheet.

The Investigator is responsible for reviewing and signing all laboratory reports. The signed clinical laboratory reports will serve as source documents and should include the Investigator's assessment of clinical significance of out of range/abnormal laboratory values.

9.5.2 Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the patient is hospitalized; the Study Center must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the patient's consent to participate in the study
- The condition that required the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the patient's consent to participate in the study and the timing of the procedure or treatment
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission

9.5.3 Dosing Errors

Volanesorsen dosing errors should be documented as Protocol Deviations. A brief description should be provided in the deviation, including whether the patient was symptomatic (list symptoms) or asymptomatic, and the event accidental or intentional.

Dosing details should be captured on the Dosing Case Report Form. If the patient takes a dose of volanesorsen that exceeds protocol specifications and the patient is symptomatic, then the symptom(s) should be documented as an AE and be reported per Section 9.4.

Should an overdose occur, the Investigator or designee should refer to the Guidance to Investigator's section of the Investigator's Brochure and contact the Sponsor or designee within 24 hours.

9.5.4 Contraception and Pregnancy

Male patients and female patients of childbearing potential must continue to use appropriate contraception with their partners, or refrain from sexual activity, as described in Section 6.3.1.

If a patient becomes pregnant or a pregnancy is suspected, or if a male patient makes or believes that he has made someone pregnant during the study, then the Study Center staff must be informed immediately. An Initial Pregnancy Form should be submitted to the Sponsor or designee **within 24 hours** of first learning of the occurrence of pregnancy. Follow-up information including delivery or termination is reported on Follow-up Pregnancy Forms and reported within 24 hours.

Payment for all aspects of obstetrical care, child or related care will be the patient's responsibility.

Female patients: If a suspected pregnancy occurs while on the study (including follow-up), a pregnancy test will be performed. The patient with a confirmed pregnancy will be immediately withdrawn from treatment with volanesorsen. However, the patient will be encouraged to complete the post-treatment follow-up portion of the study to the extent that study procedures do not interfere with the pregnancy. Regardless of continued study participation, the study physician will assist the patient in getting obstetrical care and the progress of the pregnancy will be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the Study Center and Sponsor may require access to the mother and infant's medical records for an additional 8 weeks after birth.

Male patients: The progress of the pregnancy in a male patient's partner should be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, **the Study Center and Sponsor may request access to the mother and infant's medical records for an additional 8 weeks after birth**. Follow-up will be performed to the extent permitted by applicable regulations and privacy considerations.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints

For fasting lipid measurements, the values at Month 3 analysis time point are defined as the average of Week 12 (Day 78) and Week 13 (Day 85) fasting assessments, the values of Month 6 analysis time point is at the end of Month 6 are defined as the average of Week 25 (Day 169) and Week 26 (Day 176) fasting assessments, and the values at the Month 12 analysis time point are defined as the average of Week 50 (Day 344) and Week 52 (Day 358) fasting assessments.

10.1.1 Efficacy Endpoints

- Percent change and absolute change from baseline in fasting TG
- Frequency and severity of patient reported abdominal pain during the treatment period
- Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-HDL-C, apoB, HDL-C, apolipoprotein A-1 (apoA-1), VLDL-C, and LDL-C
- Percent change from baseline in fasting total apolipoprotein C-III
- Change in blood viscosity (may be evaluated)
- Quality of Life questionnaires (EQ-5D, SF-36)
- Adjudicated acute pancreatitis event rate
- Other symptoms: eruptive xanthoma, lipemia retinalis

10.1.2 Safety Endpoints

- Adverse events including adjudicated events of pancreatitis and MACE
- Vital signs and weight
- Physical examinations
- Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis)
- Echocardiography
- Electrocardiograms (ECGs)
- Use of concomitant medications
- MRIs
- Platelet aggregation (may be evaluated)

10.2 Sample Size

No sample size calculations were performed as this is an open-label study.

10.3 Populations

Full Analysis Set (FAS): All patients who are enrolled and received at least 1 dose of active Study Drug and have a baseline TG assessment. The FAS represents the practically-feasible intent-to-treat (ITT) population as delineated in ICH Guideline E9.

Per Protocol Set (PPS): Subset of the FAS who received 9 of first 13 scheduled doses of volanesorsen and with no significant protocol deviations that would be expected to affect efficacy and PD assessments. The detailed criteria will be specified and finalized prior to the final database lock.

Safety Set: All patients who are enrolled and receive at least 1 dose of volanesorsen.

PK Population: All patients who are enrolled, receive at least 1 dose of volanesorsen, and have at least 1 post first dose PK sample collected, analyzed, and reported.

10.4 Definition of Baseline

Definitions of baseline are given below for the purposes of the final analysis.

For fasting lipid measurements, 2 baselines are defined for each patient in Groups 1 and 2: Group 1 (ISIS 304801-CS6) or Group 2 (ISIS 304801-CS16) index study baseline and the baseline in this open-label study, which is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 (e.g., qualification assessments or assessments from final visit of the ISIS 304801-CS6 or ISIS 304801-CS16 index studies if used for qualification). For Group 3 patients, the baseline for fasting lipid measurements is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 in this open-label study.

For other measurements, baseline for patients on active treatment in the ISIS 304801-CS6 or ISIS 304801-CS16 index study will be the ISIS 304801-CS6 or ISIS 304801-CS16 index study baseline. For patients on placebo in the ISIS 304801-CS6 or ISIS 304801-CS16 index study and Group 3 patients, baseline will be the last non-missing assessment prior to the first dose of Study Drug.

10.5 Interim Analysis

An interim analysis may be conducted after the last patient's Week 13 visit of the open-label study or after the database of the ISIS 304801-CS6 and ISIS 304801-CS16 index studies are locked and unblinded. Both safety and efficacy information from this open-label study may be summarized during this interim analysis. Efficacy analyses will be detailed in the SAP.

10.6 Planned Methods of Analysis

All eCRF data, lab data transfers, as well as any outcomes derived from the data, will be provided in the patient data listings. Patient data listings will be presented for all patients enrolled into the study. Descriptive summary statistics including n, mean, median, standard deviation, standard error, interquartile range (25th percentile, 75th percentile), and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data by treatment group of the index studies for patients on active in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies, and pooled treatment naive group which including patients on placebo in index studies and Group 3 patients.

Where appropriate, p-values will be reported. All statistical tests will be conducted using 2-sided tests with 5% Type I error rates unless otherwise stated.

TG related endpoints will be assessed in the FAS and PPS, and all other efficacy endpoints will be assessed in the FAS. All safety assessments will be performed on the Safety Set. PK endpoints will be assessed in the PK Set as applicable.

10.6.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics by treatment group and overall. The patient disposition will be summarized by treatment group and overall. All patients enrolled will be included in a summary of patient disposition.

10.6.2 Safety Analysis

Treatment duration and amount of Study Drug received will be summarized by treatment group and overall.

Patient incidence rates of AEs will be tabulated by MedDRA system organ class, MedDRA preferred term, and treatment group of the index studies. Narratives of treatment-emergent deaths, serious and significant AEs, including early withdrawals due to AEs, will also be provided.

All treatment-emergent AEs, all treatment-emergent AEs potentially related to Study Drug, all treatment-emergent serious AEs, and all treatment-emergent serious AEs potentially related to Study Drug will be summarized.

Injection Site Reactions (ISRs) will be summarized by treatment group, MedDRA preferred term and severity.

Independently adjudicated events of MACE and pancreatitis will be summarized by treatment group.

Laboratory tests to ensure patient safety including chemistry panel, complete blood count (CBC) with differential, coagulation panel, IM, complement etc., will be summarized by study visits by treatment group.

These safety variables will also be presented as change and percent change from baseline over time after Study Drug administration, as appropriate.

Vital signs, weight, ECG measures, echocardiography assessments, and MRI assessments will be tabulated by treatment group.

10.6.3 Efficacy Analysis

Percent change and change from baseline to Month 3, Month 6, and Month 12 in fasting TG will be summarized by treatment group. Response rate of patients with fasting plasma TG < 750 mg/dL or achieving fasting TG $\geq 40\%$ reduction from baseline at Month 3, Month 6, and Month 12 will be summarized. Response analysis will also be conducted using a range of fasting plasma TG thresholds for determination of responder status.

Percent change and change from baseline to Month 3, Month 6, and Month 12 will also be summarized by treatment group for other fasting lipid measures including non-HDL-C, apoB, HDL-C, apoA-1, VLDL-C, and LDL-C, total cholesterol, and fasting total apoC-III.

The incremental effects of volanesorsen on lipid measures will be explored and the association between changes in lipid parameters and total amount of drug received will be examined, as appropriate.

Frequency and severity of patient reported abdominal pain, adjudicated acute pancreatitis event rate, quality of life assessments, and comparison of other symptoms including eruptive xanthomas and lipemia retinalis will be summarized by treatment group.

Additional details of the analyses to be conducted will be provided in the SAP.

10.6.4 Pharmacokinetic and Immunogenicity Analysis

10.6.4.1 Pharmacokinetic Analysis

For all patients, pre-dose and post-treatment volanesorsen plasma concentrations will be summarized using descriptive statistics by treatment group and IM status.

For patients in the PK subgroup only, non-compartmental PK analysis of volanesorsen will be carried out on each individual patient data set using data collected in the open-label study from the intensive PK subgroup, following a single-dose (i.e., single-dose PK) or multiple doses (i.e., steady-state PK), depending on their earlier treatment in the index studies (Group 1 and 2 patients). On Week 1 Day 1 of the open-label study, patients who received placebo in the index study (and all patients in Group 3) will receive the first treatment of volanesorsen (single-dose PK), while patients who received volanesorsen in the index studies had been on volanesorsen treatment for 12 months (ISIS 304801-CS6) or 6 months (ISIS 304801-CS16), thus the PK data collected from these patients reflect steady-state PK. The maximum observed drug concentration (C_{max}) and the time taken to reach C_{max} (T_{max}) will be obtained directly from the concentration-time data. Area under the plasma concentration-time curve from time zero to 24 hours ($AUC_{0\text{-}24h}$) will be calculated using the linear trapezoidal rule. Apparent systemic (plasma) clearance after SC administration ($CL_{0\text{-}24h}$ /F) will be calculated from $CL_{0\text{-}24h}/F$ = Actual Dose/$AUC_{0\text{-}24h}$. Mean residence time (MRT) from time zero to 24 hours after the SC administration will be calculated from the equation, $MRT_{0\text{-}24h} = AUMC_{0\text{-}24h}/AUC_{0\text{-}24h}$, where $AUMC_{0\text{-}24h}$ is the area under the moment plasma concentration-time curve from time zero to 24 hours after the SC administration. Other PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist.

Plasma PK parameters will be summarized using descriptive statistics by treatment group and IM status. Additional details regarding the PK analysis will be described in the SAP.

Population PK, PK/PD, and covariate analysis may be performed if deemed appropriate, and results will be reported separately.

10.6.4.2 Immunogenicity Analysis

Immunogenicity (IM) results (screen positive/negative, confirmed positive/negative or not evaluable, and when applicable, titer of anti-volanesorsen antibodies) before, during, and after

treatment with Study Drug (volanesorsen) (i.e., sample [anti-drug antibody] ADA status) will be listed by their prior treatment in study ISIS 304801-CS6 or ISIS 304801-CS16 (Groups 1 and 2) and study day. Subject ADA status (positive/negative or not evaluable) for all evaluable patients, along with the study day associated with the first positive IM status emerged (T_{first}, i.e., onset of ADA development), the last positive IM status observed (T_{last}), the last ADA sample collection day, and subject - peak titer if applicable, will be listed by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16 (Groups 1 and 2) and study day. Subjects with positive anti-volanesorsen antibody status may be further classified (when applicable) as being either 'persistent', 'transient', or 'not determinable', if deemed appropriate.

Additionally, the sample and subject IM incidence (number) and incidence rate (percent) will be summarized as the total number and percent of evaluated subjects with antibody negative, positive, and unknown status by treatment group. Furthermore, onset and titer of the ADA response, if applicable, will be summarized as median, quartiles (25% and 75%), and range.

Additional details regarding the IM data analysis will be described in the SAP.

Potential relationships between immunogenicity results (e.g., IM status) and selected efficacy (e.g., % change in fasting TG from baseline at 3-, 6-, and 12-month endpoints), safety, and PK (e.g., C_{trough}) measures will be evaluated using graphical analysis and statistical analysis. These analyses will be either conducted and included in the study report, or data pooled and analyzed from all available Phase 2 and 3 studies and reported separately.

11. INVESTIGATOR'S REGULATORY OBLIGATIONS

11.1 Informed Consent

The written informed consent document should be prepared in the language(s) of the potential patient population, based on an English version provided by the Sponsor.

Before a patient's participation in the trial, the Investigator is responsible for obtaining written informed consent from the patient after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific qualification procedures or any Study Drug are administered. The patient must be given sufficient time to consider whether to participate in the study.

The acquisition of informed consent and the patient's agreement or refusal to notify his/her primary care physician should be documented in the patient's medical records and the informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion (not necessarily an Investigator). The original signed informed consent form should be retained in the Study Master File and in any other locations required by institutional policy, and a copy of the signed consent form should be provided to the patient.

11.2 Ethical Conduct of the Study

The Guidelines of the World Medical Association (WMA) Declaration of Helsinki dated October 2002 the applicable regulations and guidelines of current Good Clinical Practice (GCP)

as well as the demands of national drug and data protection laws and other applicable regulatory requirements will be strictly followed.

11.3 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent form, other written patient information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by the Sponsor before recruitment of patients into the study and shipment of volanesorsen. A copy of the written approval of any other items/materials that must be approved by the Study Center or IEC/IRB must also be received by the Sponsor before recruitment of patients into the study and shipment of Study Drug. The Investigator's Brochure must be submitted to the IEC/IRB for acknowledgement.

The Investigator must submit to and, where necessary, obtain approval from the IEC/IRB, for all subsequent protocol amendments and changes to the informed consent document. The Investigator should notify the IEC/IRB of deviations from the protocol in accordance with ICH GCP Section 4.5.2. The Investigator should also notify the IEC/IRB of serious adverse events occurring at the Study Center and other adverse event reports received from the Sponsor, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study. Copies of the Investigator's reports, all IEC/IRB submissions and the IEC/IRB continuance of approval must be sent to the Sponsor.

11.4 Patient Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained. On the case report forms (CRF) or other documents submitted to the Sponsor, patients should be identified by unique initials and a patient study number only. Documents that are not for submission to the Sponsor (e.g., signed informed consent forms) should be kept in strict confidence by the Investigator.

In compliance with Federal and local regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the patient to permit named representatives to have access to his/her study-related records without violating the confidentiality of the patient.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments

Protocol amendments must be made only with the prior approval of the Sponsor. Agreement from the Investigator must be obtained for all protocol amendments and amendments to the informed consent document. The regulatory authority and IEC/IRB must be informed of all amendments and give approval for any amendments likely to affect the safety of the patients or

the conduct of the trial. The Investigator **must** send a copy of the approval letter from the IEC/IRB to the Sponsor.

12.2 Study Termination

The Sponsor reserves the right to terminate the study according to the terms of the site contract. The Investigator reserves the right to terminate their participation in the study, according to the terms of the site contract. The Investigator/Sponsor should notify the IEC/IRB in writing of the trial's completion or early termination and send a copy of the notification to the Sponsor.

12.3 Study Documentation and Storage

An electronic case report form (eCRF) utilizing an Electronic Data Capture (EDC) application will be used for this study.

The Investigator should ensure that all appropriately qualified persons to whom he/she has delegated trial duties are recorded on a Sponsor-approved Delegation of Site Responsibilities Form.

Source documents are original documents, data, and records from which the patient's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, imaging, and correspondence. In this study, CRFs may not be used as source documents.

The Investigator and Study Center staffs are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation in accordance with Section 8 of the ICH Guidelines (E6), suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Elements should include:

- Patient files containing completed CRFs, informed consents, and supporting copies of source documentation
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation and all correspondence to and from the IEC/IRB and the Sponsor
- If volanesorsen supplies are maintained at the Study Center, proof of receipt, volanesorsen Accountability Record, Return of volanesorsen for Destruction, final study volanesorsen reconciliation, and all volanesorsen-related correspondence

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

No study document should be destroyed without prior written agreement between the Sponsor or and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor.

12.4 Study Monitoring

The Sponsor representative and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting

the various records of the trial (e.g., CRFs and other pertinent data) provided that patient confidentiality is respected.

The Sponsor monitor is responsible for inspecting the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to patient medical records and other study-related records needed to verify the entries on the CRFs.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's Clinical Quality Assurance Department. Inspection of Study Center facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the trial conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

To ensure the quality of clinical data a clinical data management review will be performed on patient data received by the Sponsor. During this review, patient data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or Study Center notifications will be sent to the Study Center for completion and return to Sponsor.

The Principal Investigator will sign and date the indicated places on the CRF. These signatures will indicate that the principal Investigator inspected or reviewed the data on the CRF, the data queries, and the Study Center notifications, and agrees with the content.

12.5 Language

Case report forms must be completed in English. Generic names for concomitant medications should be recorded in English if possible, unless it is a combination drug, then record the trade name in English.

All written information and other material to be used by patients and investigative staff must use vocabulary and language that are clearly understood.

12.6 Compensation for Injury

The Sponsor maintains appropriate insurance coverage for clinical trials and will follow applicable local compensation laws. Patients will be treated and/or compensated for any study-related illness/injury in accordance with the information provided in the Compensation for Injury section of the Informed Consent document.

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14. APPENDICES

Appendix A Schedule of Procedures

Appendix A Schedule of Procedures

Study Period		Screen/ Run In[a]	Qual[a]	Treatment Period																						Post Treatment Follow-up		
Study Week		-8 to -2	-2 to -1	Wk 1		Wk 4	Wk 6	Wk 8	Wk 10	Month 3		Wk 15 & 17	Wk 19	Wk 21 & 23	Month 6		Wk 28 & 30	Wk 32	Wk 34 & 36	Wk 38	Wk 40 & 42	Wk 44	Wk 46 & 48	Month 12		Wk 54 & 56	Wk 58	Wk 65
										Wk 12	Wk 13				Wk 25	Wk 26								Wk 50	Wk 52 or ET			
Study Day		-56 to -15	-14 to -7	1	2	22	36	50	64	78	85	99 & 113	127	141 & 155	169	176	190 & 204	218	232 & 246	260	274 & 288	302	316 & 330	344	358	372 & 386	400	449
Visit Window+/- Days		0	0	0	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	7	7
Informed Consent		X	X																									
Outpatient Visit		X	X	X	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X	X[l]	X[l]	X[l]	X[l]	X	X[l]	X[l]	X[l]	X	X[l]	X[l]	X[l]	X[l]	X	X[l]	X[l]	X
Inclusion/Exclusion Criteria		X	X																									
Medical History[b]		X																										
Vital Signs + body weight (+ height on Day 1 only)		X	X	X		X		X			X					X				X					X			X
Physical Examination		X		X							X					X				X					X			X
12- lead ECG (triplicate)		X									X					X				X					X			X
MRI (liver/spleen)		X																							X[m]			
Echocardiography		X														X[m]									X[m]			
Blood Draw (Fasting)[d]	Chemistry Panel	X	X	X		X		X			X		X			X		X		X		X			X		X	X
	CBC with Differential[c]	X	X	X — Platelets are assessed each calendar week, visits do not have specified windows to allow flexibility of scheduling.																								X
	Serum Lipid Panel	X	X	X		X		X		X	X				X	X				X				X	X			X
	Blood viscosity[e]			X							X					X									X			
	Platelet aggregation[e]		X	X							X					X									X			
	Coagulation (aPTT, PT, INR)	X	X					X			X					X				X					X			
	Hepatitis B, C, HIV	X																										
	hsCRP, HbA1c, FPG, and de-lipidated free glycerol	HbA1c		X							X					X									X			X
	Sedimentation Rate			X							X					X									X			X
	Complement (C5a, Bb)			X							X					X									X			X
	Troponin I	X		X							X					X									X			X
	Platelet Bound Autoantibodies[e]			X																								
	Plasma PK - Volanesorsen			X[n]	X	X		X			X					X				X					X			X
	Anti-Volanesorsen Antibodies			X		X		X			X					X				X					X			X
	FSH (women only, if applicable)	X																										
	Serum Pregnancy Test[f]	X	X			X		X			X		X			X		X		X		X			X		X	X

Appendix A Schedule of Procedures *Continued*

Study Period		Screen/ Run In[a]	Qual[a]	Treatment Period																						Post Treatment Follow-up		
Study Week		-8 to -2	-2 to -1	Wk 1		Wk 4	Wk 6	Wk 8	Wk 10	Month 3		Wk 15 & 17	Wk 19	Wk 21 & 23	Month 6		Wk 28 & 30	Wk 32	Wk 34 & 36	Wk 38	Wk 40 & 42	Wk 44	Wk 46 & 48	Month 12		Wk 54 & 56	Wk 58	Wk 65
										Wk 12	Wk 13				Wk 25	Wk 26								Wk 50	Wk 52 or ET			
Study Day		-56 to -15	-14 to -7	1	2	22	36	50	64	78	85	99 & 113	127	141 & 155	169	176	190 & 204	218	232 & 246	260	274 & 288	302	316 & 330	344	358	372 & 386	400	449
Visit Window+/- Days		0	0	0	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	7	7
Blood Draw (Fasting)[d]	Archive blood sample for potential gene sequencing related to hypertriglyceridemia (Group 3; Group 2 if not available from index study)[i]	X																										
	Archived Serum & Plasma Samples[g]			X				X			X					X									X			X
Urinalysis[d]		X	X	X°		X		X			X°		X°			X°		X°		X°		X°			X°		X°	X°
Fundus Photography[h]		X																							X[m]			
Genetic testing for FCS diagnosis (if not available in medical history)[i]		X																										
Weekly Study Drug: SC Injection				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Symptom Diary (weekly)		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Assessment(s)				X							X					X									X			X
Food/Drink Diary (quarterly)[j]				X							X					X									X			X
Diet/Alcohol Counseling[k]		X	X	X		X		X			X					X				X					X		X	X
Adverse Events		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a Screening and Qualification (Group 3) procedures performed (Please refer to Sections 3.4, 4.1, and 6.1.2)

b Patient charts will be reviewed in order to collect data for events of acute pancreatitis or suspected pancreatitis in the patient's medical history. Chart review may be conducted at any time during the study. These events will be adjudicated in the same manner as for events of pancreatitis during the study

c Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1 week and the result must be reviewed by the Investigator and confirmed to be acceptable before dosing can continue. All platelet count results will be promptly reviewed by the Investigator to determine if the count has met a stopping rule, or the dose reduction rule of 100,000/mm^3, or the dose pause rule of 75,000/mm^3. Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor

Appendix A Schedule of Procedures *Continued*

Legend Text *Continued*

d Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours. During treatment period urine and blood samples will be collected prior to Study Drug administration. Does not apply to 24-hour PK blood draw

e May be done. Blood viscosity and platelet aggregation in volanesorsen-treatment naïve patients only

f Females of childbearing potential only

g Serum and plasma samples will be collected and stored for follow-up exploration of laboratory findings and/or adverse events (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.) in this or subsequent clinical studies of volanesorsen

h If possible, fundus photography should be completed prior to administration of the first dose of Study Drug (Group 2 [ISIS 304801-CS16 roll-over patients] and Group 3) and repeated at Week 52 (Please refer to Section 6.2.2.2)

i Genetic testing can be conducted for study qualification (Group 2 [ISIS 304801-CS16 roll-over patients] and Group 3); genetic testing will only be conducted if allowed in the geographic region and only after the patient has given specific written informed consent for genetic testing

j In addition to diary, patients will be contacted at random times during the study to review their current eating and drinking habits

k To reinforce compliance to the diet and alcohol restrictions. Random diet/alcohol assessments (phone visits) will also be performed by dietician or study personnel

l Assessments and procedures to be conducted by either a home healthcare nurse, or the Study Center as arranged by the Study Center personnel

m A ± 7-day window is allowed for MRI, echocardiography procedures and fundus photography

n Full or abbreviated PK profile (see Appendix C)

o Expanded urinalysis (see Appendix B)

Appendix A Schedule of Procedures – Extended Treatment Period

Study Period		Treatment Period																Post-Treatment Follow-up		
Study Week		Wk 54 & 56	Wk 58	Wk 60 & 62	Mo 15 Wk 64	Wk 66 & 68	Wk 70	Wk 72 & 74	Mo 18 Wk 76	Wk 78 & 80	Wk 82	Wk 84, 86, & 88	Mo 21 Wk 90	Wk 92 & 94	Wk 96	Wk 98, 100 & 102	Mo 24 Wk 104	Wk 106 & 108	Wk 110	Mo 27 Wk 117
Study Day		372 & 386	400	414 & 428	442	456 & 470	484	498 & 512	526	540 & 554	568	582, 596 & 610	624	638 & 652	666	680, 694 & 708	722	736 & 750	764	813
Visit Window+/- Days		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	7	7
Outpatient Visit		X[f]	X[f]	X[f]	X	X[f]	X[f]	X[f]	X	X[f]	X[f]	X[f]	X	X[f]	X[f]	X[f]	X	X[f]	X[f]	X
Vital Signs (+ body weight)					X				X				X				X			X
Physical Examination									X								X			
12- lead ECG (triplicate)									X								X			
Urinalysis(including P/C ratio)			X		X		X		X		X		X		X		X		X	X
Blood Draw (Fasting)[b]	Chemistry Panel		X		X		X		X		X		X		X		X		X	X
	CBC with Differential[a]	X Platelets are assessed each calendar week, visits do not have specified windows to allow flexibility of scheduling.																		X
	Serum Lipid Panel				X				X				X				X			X
	Coagulation (aPTT, PT, INR)				X				X				X				X			
	Troponin I				X				X				X				X			X
	Plasma PK - ISIS 304801[c]								X								X			X
	Anti-ISIS 304801 Antibodies								X								X			X
	Serum Pregnancy Test[d]		X		X		X		X		X		X		X		X		X	X
Weekly Study Drug: SC Injection		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Diet/Alcohol Counseling[e]					X				X				X				X			
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Appendix A Schedule of Procedures – Extended Treatment Period *Continued*

Legend Text

a Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1 week and the result must be reviewed by the Investigator and confirmed to be acceptable before dosing can continue. All platelet count results will be promptly reviewed by the Investigator to determine if the count has met a stopping rule, or the dose reduction rule of 100,000/mm^3, or the dose pause rule of 75,000/mm^3. Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor

b Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours. During treatment period urine and blood samples will be collected prior to Study Drug administration

c Abbreviated PK collection (see Appendix C)

d Females of childbearing potential only

e To reinforce compliance to the diet and alcohol restrictions

f Assessments and procedures to be conducted by either a home healthcare nurse, or the Study Center as arranged by the Study Center personnel

Appendix B List of Laboratory Analytes

Appendix B List of Laboratory Analytes

Based on emerging data from this or future studies, additional tests not listed below may be performed on stored samples to better characterize the profile of volanesorsen or other similar oligonucleotides.

Clinical Chemistry Panel

- Sodium
- Potassium
- Chloride
- Bicarbonate
- Total protein
- Albumin
- Calcium
- Magnesium
- Phosphorus
- Glucose
- BUN
- Creatinine
- Uric Acid
- Total bilirubin
- Direct (conjugated) bilirubin
- Indirect (unconjugated) bilirubin
- ALT
- AST
- Alkaline phosphatase

Screening Tests (Group 3)

- Hepatitis B surface antigen
- Hepatitis C antibody
- HIV antibody
- FSH (women only)
- Serum βhCG (women only)

Coagulation

- aPTT (sec)
- PT (sec)
- INR

Lipid Panel

- Total Cholesterol
- LDL-C
- HDL-C
- Triglycerides
- Non-HDL-C
- VLDL-C
- apoA-1
- apoB
- apoC-III

Hematology

- Red blood cells
- Hemoglobin
- Hematocrit
- MCV, MCH, MCHC
- Platelets
- White blood cells
- WBC Differential (% and absolute)
  - Neutrophils
  - Eosinophils
  - Basophils
  - Lymphocytes
  - Monocytes

Pharmacokinetics[1] & Immunogenicity

- Volanesorsen levels in plasma
- Anti-volanesorsen antibodies in plasma

Other Assessments

- hsCRP
- Sedimentation Rate
- C5a, Bb
- Troponin I[2]
- CK-MB[2]
- Platelet Bound Autoantibodies[3]
- De-lipidated free glycerol
- HbA1c, FPG
- Blood viscosity[3]

Urinalysis

- Color
- Appearance
- Specific gravity
- pH
- Protein
- Blood
- Ketones
- Urobilinogen
- Glucose
- Bilirubin
- Leukocyte esterase
- Nitrate
- Microscopic examination[4]

Additional Measures for Expanded Urinalysis

- Total protein (quantitative)
- Microalbumin
- β2-microglobulin

Platelet Function

- Platelet aggregation[3]

1 Plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, IM testing (or possibly for purposes of IM assay development and/or validation), or to assess other actions of volanesorsen with plasma constituents

2 All abnormal troponin samples will be rerun at the central laboratory and also analyzed for CK-MB

3 May be done

4 Will be performed on abnormal findings unless otherwise specified

Appendix C Pharmacokinetic Sampling Schedule

Appendix C Pharmacokinetic Sampling Schedule

Blood samples for the determination of plasma volanesorsen concentrations will be collected prior to dosing, and at various times throughout the dosing and post-treatment follow-up period as noted in the tables below.

PK Sampling Schedule (All Patients except PK Subgroup)

Week	**Wk 1**	**Wk 4**	**Wk 8**	**Wk 13**	**Wk 26**	**Wk 38**	**Wk 52**	**Wk 65#**
Study Day	**D1**	**D22**	**D50**	**D85**	**D176**	**D260**	**D358**	**D449**
Visit Window +/- Days	0	2	2	2	2	3	2	7
Time Point	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime

Week 65 PK collection will be omitted for patients continuing to receive volanesorsen beyond Week 52

PK Sampling Schedule (PK Subgroup only*)

Week	**Wk 1**	**Wk 1**	**Wk 4**	**Wk 8**	**Wk 13**	**Wk 26**	**Wk 38**	**Wk 52**	**Wk 65#**
Study Day	**D1**	**D2**	**D22**	**D50**	**D85**	**D176**	**D260**	**D358**	**D449**
Visit Window +/- Days	0	0	2	2	2	2	3	2	7
Time Point	Pre-dose, 1, 2, 3, 4, 6, 8, and 12 hrs post-dose	24 hrs post-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime

* Patients at selected sites will be asked to participate in the extended 24-hour PK profile beginning on Study Day 1. Participation is optional

Week 65 PK collection will be omitted for patients continuing to receive volanesorsen beyond Week 52

PK Sampling Schedule (Extended Treatment Period)

Week	**Wk 76**	**Wk 104**	**Wk 117**
Study Day	**D526**	**D722**	**D813**
Visit Window +/- Days	2	2	7
Time Point	Pre-dose,	Pre-dose	Anytime

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

The following grading recommendations for adverse events relating to lab test abnormalities are based upon the **Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010**

Adverse Event	Mild	Moderate	Severe
Hematology			
aPTT prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage
Eosinophils increased[†]	650 – 1,500 cell/mm^3	1,501 - 5,000 cell/mm^3	>5,000 cell/mm^3
Fibrinogen decreased	<1.0 - 0.75 x LLN or <25% decrease from baseline	<0.75 - 0.5 x LLN or 25 - <50% decrease from baseline	<0.5 x LLN or ≥50% decrease from baseline
Hemoglobin decreased (Anemia)	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated
Hemoglobin increased	Increase in >0 - 2 g/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 g/dL above ULN or above baseline if baseline is above ULN	Increase in >4 g/dL above ULN or above baseline if baseline is above ULN
INR increased	>1 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation
Lymphocyte count decreased	<LLN - 800/mm^3; <LLN - 0.8 x 10^9/L	<800 - 500/mm^3; <0.8 - 0.5 x 10^9 /L	<500 /mm^3; <0.5 x 10^9 /L
Lymphocyte count increased	-	>4000/mm^3 - 20,000/mm^3	>20,000/mm^3
Neutrophil count decreased	<LLN - 1500/mm^3; <LLN - 1.5 x 10^9 /L	<1500 - 1000/mm^3; <1.5 - 1.0 x 10^9 /L	<1000/mm^3; <1.0 x 10^9 /L
Platelet count decreased	<LLN - 75,000/mm^3; <LLN - 75.0 x 10^9 /L	<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9 /L	<50,000/mm^3; <50.0 x 10^9 /L
White blood cell decreased	<LLN - 3000/mm^3; <LLN - 3.0 x 10^9 /L	<3000 - 2000/mm^3; <3.0 - 2.0 x 10^9 /L	<2000/mm^3; <2.0 x 10^9 /L
Chemistry			
Acidosis	pH <normal, but >=7.3	-	pH <7.3
Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Alkalosis	pH >normal, but ≤7.5	-	pH >7.5
Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 x ULN
Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

Adverse Event	Mild	Moderate	Severe
Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer
CD4 lymphocytes decreased	<LLN - 500/mm^3; <LLN - 0.5 x 10^9 /L	<500 - 200/mm^3; <0.5 - 0.2 x 10^9 /L	<200/mm^3; <0.2 x 10^9 /L
CPK increased*	>ULN - <6 ULN	6 - 10 x ULN	>10 x ULN
Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 x ULN
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 mg/dL; >3.1 mmol/L; Ionized calcium >1.6 mmol/L; hospitalization indicated
Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 mg/dL; >13.9 mmol/L; hospitalization indicated
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0; hospitalization indicated
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 mg/dL; >1.23 mmol/L
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 mmol/L; hospitalization indicated
Hyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 mg/dL; <1.75 mmol/L; Ionized calcium <0.9 mmol/L; hospitalization indicated
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 mg/dL; <3.0 mmol/L	<40 mg/dL (<2.2 mmol/L) AND requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions‡
Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 mmol/L; hospitalization indicated
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 mg/dL; <0.4 mmol/L
Hyponatremia	<LLN - 130 mmol/L	-	<130 mmol/L
Hypophosphatemia	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 mg/dL; <0.6 mmol/L
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

Adverse Event	Mild	Moderate	Severe
Urine			
Proteinuria Adults Children	1+ proteinuria; urinary protein <1.0 g/24 hrs -	2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs; Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Urinary protein ≥3.5 g/24 hrs; Urine P/C >1.9
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated

[†]Grading for this parameter is derived from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007

[*]Grading for this parameter is derived from the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0, Nov 2014

[‡]Modified for consistency with the ADA and Endocrine Society Guidelines (Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. Diabetes Care 2013;36:1384-95)

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ISIS 304801-CS7

The APPROACH Open-Label Study

Volanesorsen (ISIS 304801)

An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol Amendment 7 - France – 3 February 2017

EudraCT No: 2015-003755-21

ISIS 304801-CS7

The APPROACH Open-Label Study

Volanesorsen (ISIS 304801)

An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol Amendment 7 - France – 3 February 2017

Protocol History:

Original Protocol:	28 August 2015
Protocol Amendment 1:	2 February 2016
Protocol Amendment 2:	22 April 2016
Protocol Amendment 3:	9 May 2016
Protocol Amendment 4:	6 June 2016
Protocol Amendment 5:	19 August 2016
Protocol Amendment 6:	16 September 2016

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Ionis Protocol Number: ISIS 304801-CS7

Protocol Amendment 7 - France

EudraCT No: 2015-003755-21

Clinical Phase: 3

The APPROACH Open-Label Study

Volanesorsen (ISIS 304801)

An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

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Date: 3 February 2017

Confidentiality Statement

This document contains confidential information of Ionis Pharmaceuticals, Inc., that must not be disclosed to anyone other than the recipient study staff and members of the independent ethics committee, institutional review board, or authorized regulatory agencies. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc.

Protocol Signature Page

Protocol Number: ISIS 304801-CS7

Protocol Title: An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Amendment: Amendment 7 - France

Date: 3 February 2017

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)", dated 3 February 2017, and agree to conduct the study as described herein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice (E6).

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc.

Investigator's Signature

Investigator's Name *(please print)* Date (DD Month YYYY)

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PROTOCOL AMENDMENT

Protocol Number: ISIS 304801-CS7

Protocol Title: An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Amendment Number: 7 - France

Amendment Date: 3 February 2017

The purpose of this protocol amendment is to implement the following modifications to Protocol ISIS 304801-CS7 Amendment 6 dated 16 September 2016:

1. To exclude enrollment of FCS patients in this open-label study who did not participate in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies
2. To add post heparin plasma LPL activity of ≤ 20% of normal in medical history as an inclusion criteria for ISIS 304801-CS16 (Group 2) patients as has been allowed for ISIS 304801–CS6 (Group 1) patients

Minor changes (not included in the list of changes below) have been made throughout the protocol to correct errors and/or to improve the overall clarity of the original protocol but these changes do not impact subject safety, exposure, or the overall study design.

The following table provides a summary list of major changes to the protocol:

Protocol Section	Description of Change	Rationale
Protocol Synopsis: Study Design 3.1 Study Design	**Was** This is a multi-center open-label study of: Group 1: ISIS 304801-CS6 (index study) roll over FCS patients Group 2: ISIS 304801-CS16 (index study) roll over FCS patients Group 3: FCS patients who did not participate in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies **Is** This is a multi-center open-label study of: Group 1: ISIS 304801-CS6 (index study) roll over FCS patients Group 2: ISIS 304801-CS16 (index study) roll over FCS patients	To exclude enrollment of FCS patients who did not participate in an index study from this open label study

Protocol Section	Description of Change	Rationale
Protocol Synopsis: Study Population 5.1 Inclusion Criteria	**Was** 3. Groups 1 and 2: Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement. Groups 2 and 3: Patients must also meet the following criteria in order to enter into the open-label study: a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L) b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) by documentation of the following: • Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1) c. Group 2: Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 index study Group 3: Fasting TG ≥ 750 mg/dL at Screening for this open-label study **Is** 3. Groups 1 and 2: Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement. Group 2: Patients who enrolled in ISIS 304801-CS16 must also meet the following criteria in order to enter into the open-label study: a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L) b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) by documentation of the following: • Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1) • Post heparin plasma LPL activity of ≤ 20% of normal in medical history c. Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 index study	To define the inclusion criteria for each group of patients. To add LPL activity of ≤ 20% of normal in medical history as an inclusion criteria for Group 2 patients as has been allowed for Group 1 patients
Protocol Synopsis: Study Population 5.2 Exclusion Criteria	**Was (noted throughout Exclusion Criteria)** Screening* *(Group 3) or Qualification (Groups 1 and 2) **Is (noted throughout Exclusion Criteria)** Qualification	To distinguish that patients who are rolling over from an index study will have Qualification assessments

Protocol Section	Description of Change	Rationale
Protocol Synopsis: Study Visit Schedule and Procedures 3.4 Overall Study Duration and Follow-up Study Design and Treatment Schema Appendix A	**Was** The study for an individual patient will generally consist of the following periods: • Group 1 and 2 patients (participated in ISIS 304801-CS6 or ISIS 304801-CS16 index study): A qualification period of up to 2 weeks (unless approved by the Sponsor). Please refer to Section 4.1 and Appendix A. • Group 3 patients (did not participate in an index study): An up to 8-week screening and qualification period, including a diet stabilization period of at least 6 weeks (screening and diet stabilization period may be reduced, per Sponsor approval, if the patient is following a diet for optimal control of TGs and disease management prior to screening). Please refer to Section 6.1.2 and Appendix A. • All patients: o A 52-week treatment period during which volanesorsen will be administered as a once weekly SC injection A 13-week post-treatment evaluation period **Is** The study for an individual patient will generally consist of the following periods: • A qualification period of up to 2 weeks (unless approved by the Sponsor). Please refer to Section 4.1 and Appendix A. • A 52-week treatment period during which volanesorsen will be administered as a once weekly SC injection • A 13-week post-treatment evaluation period	To remove FCS patients who did not participate in an index study from the study schedule
4.1 Screening/Qualification	**Was** Groups 1 and 2 (Qualification): During the qualification period, the eligibility of the patient to enroll in the open-label study will be determined. Final assessments from the ISIS 304801-CS6 or ISIS 304801-CS16 studies may be used for qualification. A period of up to 2 weeks after completion of the ISIS 304801-CS6 or ISIS 304801-CS16 index studies (unless approved by the Sponsor) is given to complete qualification. Qualified patients will retain the unique patient identification number that was assigned to them during the ISIS 304801-CS6 or ISIS 304801-CS16 index studies. The patient identification number will be used to identify the patient throughout the extension trial and must be used on all study documentation related to that patient. The patient identification number must remain constant throughout the extension trial. Group 3 (Screening and Qualification): At the time of consent, the patient will be considered enrolled into the study and will be assigned a unique screening number before any study procedures, including screening procedures, are performed. At the time of enrollment, patients will be assigned a unique patient identification number. This number will be used to identify the patient throughout the trial and must be used on all study documentation related to that patient. The screening number and patient identification number must remain constant throughout the entire trial. In the event the patient is re-consented and re-screened the patient must be given a new screening number. Screening numbers and patient identification numbers, once assigned, will not be re-used.	To remove FCS patients who did not participate in an index study from Screening/ Qualification

Protocol Section	Description of Change	Rationale
4.1 Screening/Qualification *Continued*	**Is** During the qualification period, the eligibility of the patient to enroll in the open-label study will be determined. Final assessments from the ISIS 304801-CS6 or ISIS 304801-CS16 studies may be used for qualification. A period of up to 2 weeks after completion of the ISIS 304801-CS6 or ISIS 304801-CS16 index studies (unless approved by the Sponsor) is given to complete qualification. Qualified patients will retain the unique patient identification number that was assigned to them during the ISIS 304801-CS6 or ISIS 304801-CS16 index studies. The patient identification number will be used to identify the patient throughout the extension trial and must be used on all study documentation related to that patient. The patient identification number must remain constant throughout the extension trial.	To remove FCS patients who did not participate in an index study from Screening/ Qualification
6.1.1 Screening 6.1.2 Screening and Qualification (Group 3)	**Was** 6.1.1 Qualification (Groups 1 and 2) Please refer to Section 4.1 and Appendix A. 6.1.2 Screening and Qualification (Group 3) Before any study-specific procedures or evaluations are initiated, patients must sign and date the informed consent form. An 8-week period, including a diet stabilization period of at least 6 weeks (screening and diet stabilization period may be reduced, per Sponsor approval, if the patient is following a diet for optimal control of TGs and disease management prior to screening) is given to perform the screening evaluations. The qualification assessments will be performed at Week -2 to -1, ideally after patient eligibility has been determined, and on Study Day 1. Abnormal screening results may be retested for review by the Study Medical Monitor for eligibility purposes **Is** 6.1.1 Qualification Please refer to Section 4.1 and Appendix A.	To remove FCS patients who did not participate in an index study from Screening/ Qualification
Section 10.3 Populations	**Updated:** Full Analysis Set (FAS): All patients who are enrolled and received at least 1 dose of active Study Drug and have a baseline TG assessment. PK Population: All patients who are enrolled, receive at least 1 dose of volanesorsen, and have at least 1 post first dose PK sample collected, analyzed, and reported.	Modified to include, in the FAS, only those patients that are randomized and dosed and have a baseline TG assessment and clarified the PK Population

PROTOCOL SYNOPSIS

Protocol Title	An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Study Phase	3
Indication	Familial Chylomicronemia Syndrome
Study Objectives	To evaluate the safety and efficacy of dosing and extended dosing with volanesorsen (volanesorsen sodium 300 mg) in patients with FCS
Study Design	This is a multi-center open-label study of: Group 1: ISIS 304801-CS6 (index study) roll over FCS patients Group 2: ISIS 304801-CS16 (index study) roll over FCS patients All patients will receive volanesorsen 300 mg once per week for 52 weeks. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period. Following the Week 52 visit, patients will enter an at least 26-week post-treatment evaluation period or will participate in an expanded access program pending approval by the IRBs/IEC, and the appropriate regulatory authorities.
Number of Patients	Up to approximately 70 patients dosed
Study Population	Inclusion Criteria: 1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law 2. Age ≥ 18 years at time of informed consent 3. Groups 1 and 2: Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement. Group 2: Patients who enrolled in ISIS 304801-CS16 must also meet the following criteria in order to enter into the open-label study: a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L) b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) by documentation of the following: • Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1) • Post heparin plasma LPL activity of ≤ 20% of normal in medical history c. Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 index study 4. Able and willing to participate in a 78-week study

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	Inclusion Criteria: *Continued* 5. Satisfy 1 of the following: a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved), abstinent*, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration b. Males: Surgically sterile, abstinent* or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration * Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception Exclusion Criteria: 1. Diabetes mellitus with any of the following: a. Newly diagnosed within 12 weeks of Qualification b. HbA1c ≥ 9.0% at Qualification c. Recent change in anti-diabetic pharmacotherapy (change in dosage or addition of new medication within 12 weeks of Qualification [with the exception of ± 10 units of insulin]) d. Anticipated need to change dose or type of medication during the treatment period of the Study (with the exception of ± 10 units of insulin) e. Current use of GLP-1 agonists 2. Severe hypertriglyceridemia other than due to familial chylomicronemia syndrome 3. Active pancreatitis within 4 weeks prior to Qualification 4. History within 6 months of Qualification of acute or unstable cardiac ischemia (myocardial infarction, acute coronary syndrome, new onset angina), stroke, transient ischemic attack or unstable congestive cardiac failure requiring a change in medication or major surgery within 3 months of Qualification

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	Exclusion Criteria: *Continued* 5. Any of the following laboratory values at Qualification a. Hepatic: • Total bilirubin > upper limit of normal (ULN), unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL • ALT > 2.0 x ULN • AST > 2.0 x ULN b. Renal: • Persistently positive (2 out of 3 consecutive tests ≥ 1+) for protein on urine dipstick. In the event of a positive test eligibility may be confirmed by a quantitative total urine protein measurement of < 500 mg/24 hrs • Persistently positive (2 out of 3 consecutive tests ≥ trace positive) for blood on urine dipstick. In the event of a positive test eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field • Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault < 50 mL/min (MDRD or CKD-EPI formulas can be used instead of Cockcroft-Gault for estimation of GFR in patients with low body weight after discussion with Sponsor Medical Monitor) c. Cardiac Troponin I > ULN at Qualification d. LDL-C > 130 mg/dL at Qualification e. Any other laboratory abnormalities which, in the opinion of the Investigator or the Sponsor, would make the patient unsuitable for inclusion 6. Uncontrolled hypertension (BP > 160/100 mm Hg) 7. History of thrombocytopenia (platelet count < 100,000/mm^3) or bleeding diathesis or coagulopathy or clinically-significant abnormality in coagulation parameters at Qualification 8. History of heart failure with NYHA greater than Class II 9. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1 10. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B 11. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated 12. Treatment with another investigational drug, biological agent, or device within 1 month of Qualification, or 5 half-lives of investigational agent, whichever is longer 13. Unwilling to comply with lifestyle requirements (Section 6.3)

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	Exclusion Criteria: *Continued* 14. Use of any of the following: a. Statins, omega-3 fatty acids (prescription and OTC), or fibrates unless on a stable dose for at least 3 months prior to Qualification and dose and regimen expected to remain constant during the treatment period. Patients taking OTC omega-3 fatty acids should make every effort to remain on the same brand throughout the study b. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to Qualification c. Systemic corticosteroids or anabolic steroids within 6 weeks prior to Qualification unless approved by the Sponsor Medical Monitor d. Atypical antipsychotic medications (e.g., olanzapine and clozapine) unless on a stable dose for at least 3 months prior to Qualification and dose and regimen expected to remain stable throughout the study e. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to Qualification and dose and regimen expected to remain constant during the treatment period f. Glybera gene therapy within 2 years prior to Qualification g. Oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, and apixaban) unless on a stable dose for at least 4 weeks prior to Qualification and regular clinical monitoring is performed h. Tamoxifen, estrogens or progestins unless on a stable dose for at least 4 months prior to Qualification and dose and regimen expected to remain constant during the treatment period i. Plasma apheresis within 4 weeks prior to Qualification or planned during the study j. Prior exposure to ISIS 304801 k. Any other medication unless stable at least 4 weeks prior to Qualification (Occasional or intermittent use of over-the-counter medications will be allowed at Investigator's discretion) 15. Blood donation of 50 to 499 mL within 30 days of Qualification or of > 499 mL within 60 days of Qualification 16. Known hypersensitivity to any of the excipients of the Study Drug (ISIS 304801 or placebo) 17. Have any other conditions, including new or worsening of existing condition, which, in the opinion of the Investigator or the Sponsor would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the study
Treatment Group	Volanesorsen 300 mg once per week
Study Drug Administration	Volanesorsen will be administered as subcutaneous (SC) injections.
Dose Adjustments	Dose adjustments, including dose interruptions and/or decreasing the dose frequency will be allowed for safety or tolerability after consultation with the Sponsor Medical Monitor.

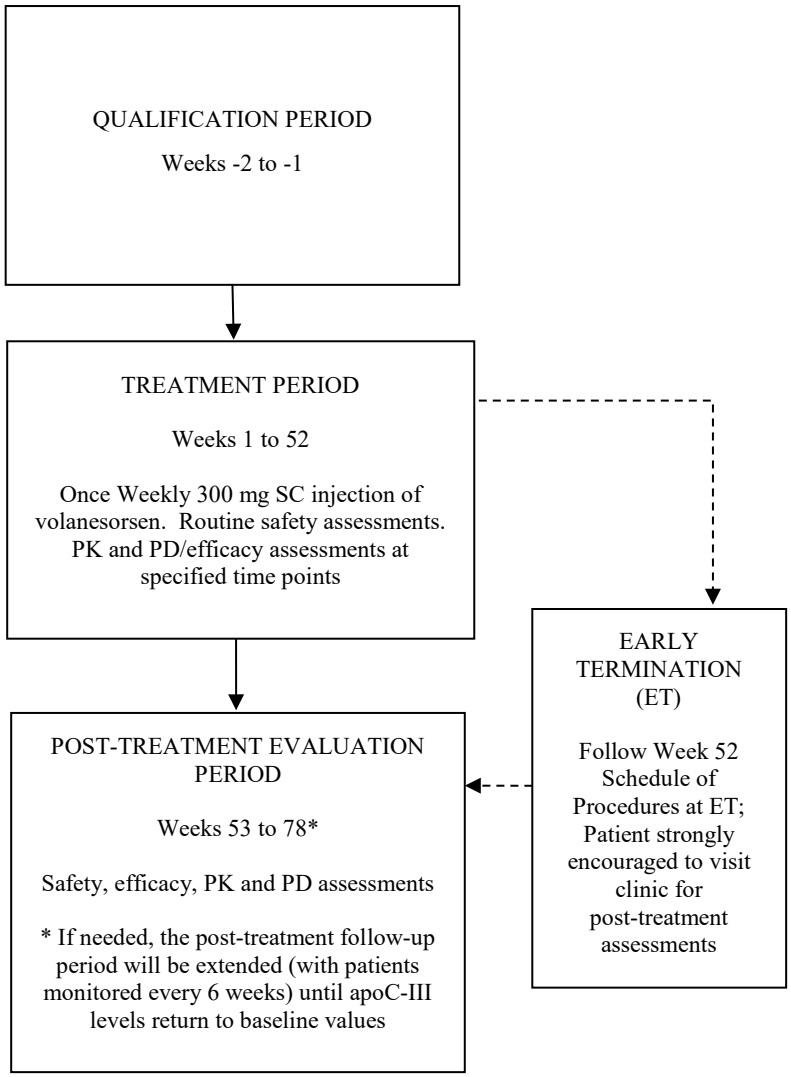
PROTOCOL SYNOPSIS *Continued*

Rationale for Dose and Schedule Selection	The dose of 300 mg once weekly was chosen for the double-blinded placebo-controlled Phase 3 index studies (ISIS 304801-CS6 and ISIS 304801-CS16) based on the pharmacodynamic and safety analysis of the Phase 2 studies (Section 2.4) which included a subset of patients with FCS. The same dose of 300 mg once weekly will be used in this open-label study of FCS patients.
Study Visit Schedule and Procedures	The study for an individual patient will generally consist of the following periods: • A qualification period of up to 2 weeks (unless approved by the Sponsor). Please refer to Section 4.1 and Appendix A • A 52-week treatment period during which volanesorsen will be administered as a once weekly SC injection • An at least 26-week post-treatment evaluation period The patients, Investigators, study staff, and the Sponsor will remain blinded to lipid data through the last patient's Week 13 visit of the open-label study or until results from the database locks for the ISIS 304801-CS6 and ISIS 304801-CS16 index studies becomes available, whichever comes first. Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), adverse events (AE), concomitant medication/procedure information, lipid panel, volanesorsen plasma concentrations, immunogenicity (IM) testing, liver/spleen magnetic resonance imaging (MRI), ECGs, echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Dietary counseling will be repeated at intervals throughout the treatment and follow-up period and a daily food/drink diary will be completed for the week prior to each quarterly visit by each patient. Following the Week 52 visit, patients will enter an at least 26-week post-treatment evaluation period or will participate in an expanded access program pending approval by the IRBs/IEC, and the appropriate regulatory authorities.
Safety and Tolerability Evaluations	Overall safety and tolerability of volanesorsen will be assessed by determining the incidence and severity of adverse and serious adverse events (including independently adjudicated events of acute pancreatitis and MACE), withdrawals due to adverse events, and changes in laboratory and other safety parameters.

PROTOCOL SYNOPSIS *Continued*

Planned Analyses	Safety Endpoints: • Adverse events including adjudicated events of acute pancreatitis and MACE • Vital signs and weight • Physical examinations • Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis) • Echocardiography • Electrocardiograms (ECGs) • Use of concomitant medications • MRIs Efficacy Endpoints: • Percent change and absolute change from baseline in fasting TG • Frequency and severity of patient reported abdominal pain during the treatment period • Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-high-density lipoprotein-cholesterol (non-HDL-C), apolipoprotein B [apoB], high-density lipoprotein-cholesterol (HDL-C), apolipoprotein A-1 [apoA-1], very-low-density lipoprotein-cholesterol (VLDL-C), and LDL-C • Percent change from baseline in fasting total apolipoprotein C-III (apoC-III) • Quality of Life questionnaires (EQ-5D, SF-36) • Adjudicated acute pancreatitis event rate • Other symptoms: eruptive xanthoma, lipemia retinalis
Pharmacokinetic Evaluations	Plasma samples will be taken from all patients for the measurement of volanesorsen as follows: trough levels (pre-dose) throughout treatment and post-treatment levels during the post-treatment follow-up period. In a subset of patients, more frequent assessment of plasma concentrations of volanesorsen will be performed to determine volanesorsen pharmacokinetic parameters. Plasma sample collection time points are detailed in Appendix A and Appendix C.
Statistical Considerations	No sample size calculations were performed as this is an open-label study.
Sponsor	Ionis Pharmaceuticals, Inc.
Collaborator	Akcea Therapeutics

STUDY DESIGN AND TREATMENT SCHEMA



STUDY GLOSSARY

Abbreviation/Acronym	Definition
ADA	anti-drug antibody
AE	adverse Event
ALP	alkaline Phosphatase
ALT	alanine Aminotransferase
ANA	antinuclear Antibody
apoA-1	apolipoprotein A-1
apoB	apolipoprotein B
apoC-III	apolipoprotein C-III
apoE	apolipoprotein E
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
CBC	complete blood count
C_{max}	maximum observed drug concentration
CRF	case report form
DNA	deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
ET	early termination
FAS	full analysis set
FCS	Familial Chylomicronemia Syndrome
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
GPIHBP1	Glycosylphosphatidylinositol-anchored HDL-binding Protein 1
HAPI	Heritability and Phenotype Intervention
HbA1c	Glycated Hemoglobin
HDL	High-Density Lipoprotein
HDL-C	High-Density Lipoprotein-Cholesterol
hsCRP	High-sensitivity C-reactive protein
ICH	International Conference on Harmonization
IDL	Intermediate density lipoprotein
IEC	Independent Ethics Committee
IM	immunogenicity
Index Studies	ISIS 304801-CS6 and ISIS 304801-CS16

STUDY GLOSSARY *Continued*

Abbreviation/Acronym	Definition
INR	International Normalized Ratio
IRB	Institutional Review Board
IXRS	Interactive Voice/Web-Response System
LDL	Low-Density Lipoprotein
LDL-C	Low-Density Lipoprotein-Cholesterol
LMF1	Lipase Maturation Factor 1
LPL	Lipoprotein Lipase
MACE	Major Acute Cardiovascular Event
MOE	2′-*O*-(2-methoxyethyl)
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NCS	not clinically-significant
NOAEL	No-Observed-Adverse-Effect Level
non-HDL-C	Non-High-Density Lipoprotein-Cholesterol
OTC	over the counter
PFS	prefilled syringe
PD	pharmacodynamic
PK	pharmacokinetic
PPS	per protocol set
PT	prothrombin time
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SUSAR	suspected unexpected serious adverse reaction
T2DM	type 2 diabetes mellitus
T_{max}	time to maximal concentration
TG	triglycerides
Treatment-emergent	occurring after first dose of Study Drug
TRL	Triglyceride-Rich Lipoproteins
ULN	upper limit of normal
VLDL	Very-Low-Density Lipoprotein
VLDL-C	Very-Low-Density Lipoprotein-Cholesterol
VLDL-TG	Lipoprotein-Triglyceride
WMA	World Medical Association

1. OBJECTIVES

The objective of the study is to evaluate the safety and efficacy of dosing and extended dosing with volanesorsen in patients with familial chylomicronemia syndrome.

2. BACKGROUND AND RATIONALE

2.1 Overview of Disease

Familial Chylomicronemia Syndrome (FCS) is an inherited disease characterized by severe hypertriglyceridemia and chylomicronemia, and risk or history of pancreatitis. It is a rare autosomal recessive disease that can be diagnosed either in childhood or adulthood.

Fasting plasma triglyceride (TG) levels in FCS patients are typically 10-fold to 100-fold above normal (1,500 to 15,000 mg/dL), despite extreme dietary fat restriction (20 g or approximately 15-20% of daily calorie intake) (Brunzell 1999-2011). Patients with FCS often present in infancy or childhood with frequent and severe abdominal pain, repetitive colicky pain, repeated episodes of potentially fatal acute pancreatitis, and failure to thrive (Brunzell 1999-2011; Tremblay et al. 2011). Physical examination frequently reveals eruptive xanthomas, lipemia retinalis and hepatosplenomegaly, and plasma from patients appears lactescent, interfering with determination of other laboratory parameters (Tremblay et al. 2011).

Patients with fasting triglyceride levels > 10 mmol/L probably have a component of chylomicronemia. Clinical diagnosis would include evidence of clinical features of chylomicronemia syndrome and secondary causes such as uncontrolled type 1 or type 2 diabetes mellitus (T2DM), hypothyroidism, poor diet, alcohol use, nephrotic syndrome or use of associated medications should be ruled out. The diagnosis of FCS may be made more specifically by genotyping or confirmation of very low or absent lipoprotein lipase (LPL) enzyme activity in post heparin plasma (Brunzell 1999-2011).

Patients with FCS carry a heavy burden of medical complications, the most serious, as described above, being an extreme risk of recurrent and potentially fatal pancreatitis. Due to the recurrent episodes of acute pancreatitis, these patients may also develop chronic pancreatitis and signs of exocrine or endocrine pancreatic insufficiency, including diabetes mellitus (Gaudet et al. 2013). While the pathophysiology underlying chylomicron-related pancreatitis has not been completely elucidated, 1 hypothesis is that large chylomicrons lodged in pancreatic capillaries are exposed to pancreatic lipase, with the subsequent release of free fatty acids through the hydrolysis of chylomicron-associated TGs. High concentrations of free fatty acids are thought to damage pancreatic cells leading to emergent pancreatitis (Yang et al. 2009; Berglund et al. 2012).

The etiology of extreme hypertriglyceridemia in FCS is considered to be ineffective triglyceride clearance, due to an extremely low level of LPL activity. LPL normally functions to hydrolyze triglycerides (TG) in chylomicrons along the luminal surface of capillaries, mainly in heart, skeletal muscle, and adipose tissue, promoting triglyceride clearance from the circulation. LPL is regulated by a number of key genes, and loss-of-function mutations in one of these genes, or the LPL gene itself, results in FCS (Surendran et al. 2012). In addition to loss of function mutations, null mutations, and nonsense mutations in the LPL gene, other genes currently identified in FCS patients, and known to directly influence LPL activity include: apolipoprotein C-II (APOC2) a cofactor for LPL (Schuster et al. 2011); apolipoprotein A-V

(APOA5) an enhancer of LPL activity (Schaap et al. 2004); lipase maturation Factor 1 (LMF1), a transmembrane protein involved in LPL maturation (Doolittle et al. 2009); glycosylphosphatidylinositol-anchored HDL-binding protein 1 (GPIHBP1), a capillary endothelial cell protein that provides a platform for LPL-mediated processing of chylomicrons (Beigneux et al. 2007).

2.2 Therapeutic Rationale

Apolipoprotein C-III (ApoC-III), a key regulator of plasma triglyceride levels, is a 79 amino acid glycoprotein synthesized principally in the liver (Ooi et al. 2008; Figure 1). ApoC-III is a major regulator of lipoprotein metabolism and plays a pivotal role in regulating plasma TG levels (Chan et al. 2008). It is a component of triglyceride-rich lipoproteins (TRLs) and a potent inhibitor of LPL (Lemieux et al. 2003). At higher concentrations apoC-III also inhibits hepatic lipase activity (Kinnunen and Ehnolm 1976), an enzyme which plays an important role in the conversion of dense very-low-density lipoprotein (VLDL) to intermediate density lipoprotein (IDL) and to LDL (Mendivil et al. 2010), as well as in the remodeling of HDL (Brown et al. 2010). In addition, increased apoC-III content adversely affects apoE-mediated hepatic uptake of TG-rich remnants (Mann et al. 1997). Thus, elevated plasma apoC-III levels are associated with impaired hydrolysis and retarded clearance of TG-rich particles, resulting in the accumulation of lipoprotein-triglyceride (VLDL-TG) and chylomicrons in plasma and the development of hypertriglyceridemia (Ito et al. 1990).

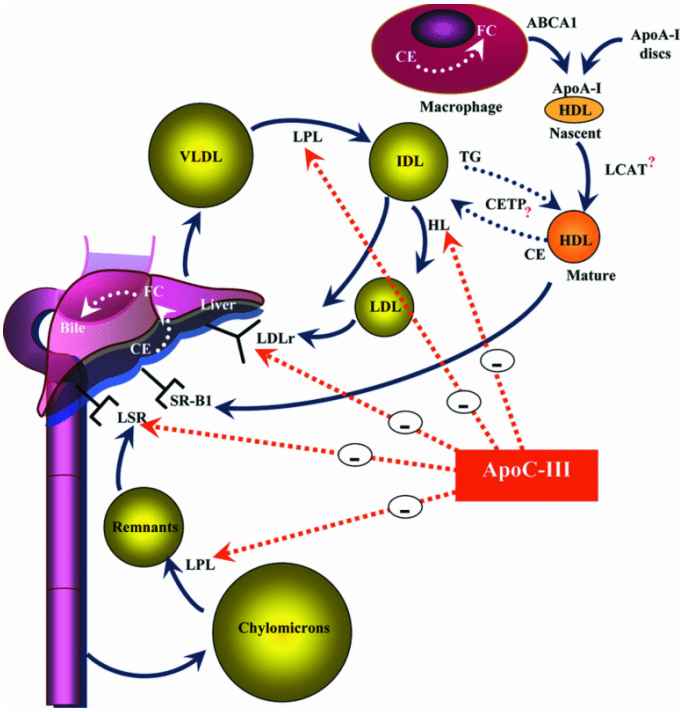


Figure 1 ApoC-III Regulates Lipoprotein Metabolism by Multiple Mechanisms

From Ooi et al. 2008; ABCA1 = ATP-binding cassette A1, apo = apolipoprotein, CE = cholesterol ester, CETP = cholesterol ester transfer protein, FC = free cholesterol, HDL = high-density lipoprotein, HL = hepatic lipase, IDL = intermediate-density lipoprotein, LCAT = lecithin cholesterol acyltransferase, LDL = low-density lipoprotein, LDLr = LDL receptor, LPL = lipoprotein lipase, LSR = lipolysis-stimulated receptor, SR-B1 = scavenger receptor B-1, TG = triglyceride, VLDL = very low-density lipoprotein.

Mechanistically, FCS is primarily a consequence of ineffective clearance of TRL. ApoC-III is a prominent component of TRL (e.g., VLDL and chylomicrons). In addition to its role in inhibiting LPL, apoC-III inhibits TRL remnant (TG-depleted remnant lipoprotein) uptake by hepatic lipoprotein receptors by steric inhibition of the interaction of apoE with these receptors.

Human genetic data have demonstrated positive phenotypic associations with loss (e.g., null or nonsense mutations) and negative effects with gain of function mutations (Atzmon et al. 2006; Pollin et al. 2008; Petersen et al. 2010). A novel nonsense mutation in the apoC-III gene was identified in the heritability and phenotype intervention (HAPI) heart study in Old Order Amish that results in lower plasma apoC-III and TG levels and lower LDL-C, increased HDL-C and reduced atherosclerosis (Pollin et al. 2008). In another study involving a group of 214 Ashkenazi Jews of advanced age (had passed or nearly reached 100 years of age), genotype analysis revealed a polymorphism in the apoC-III gene (APOC3-641CC genotype) with a clear pattern of age-dependent frequency that was associated with significantly lower levels of apoC-III protein, a favorable lipoprotein profile and increased longevity (Atzmon et al. 2006). In contrast to the Amish and Ashkenazi apoC-III polymorphisms associated with lower plasma TG, apoC-III polymorphisms associated with higher plasma TG have also been recently described (Petersen et al. 2010). In a cohort of lean (mean body mass index [BMI] = 24.7 ± 3.6 kg/m^2) Asian Indians, carriers of apoC-III variant alleles (C-482T, T-455C, or both) were noted to have significantly higher plasma apoC-III and TG levels, and decreased ability to clear postprandial plasma TG from the circulation. Taken together, the available data strongly support the development of a therapy that reduces plasma apoC-III levels in order to reduce the very high circulating triglyceride and chylomicron levels that are accompanied by increasing risk for acute pancreatitis.

Given the profound reductions in TGs observed with volanesorsen treatment in FCS patients who have no detectable LPL activity (See Section 2.3.4), and the mechanistic data available to date on apoC-III function, potential mechanisms that explain how apoC-III inhibition results in triglyceride reduction in FCS patients include: (1) enhancing the very small residual amounts of LPL activity that these patients may have, below the limit of detection of the assay in many cases (2) potentially enhanced activity of other lipases also involved in the metabolism and breakdown of TGs, such as hepatic lipase or endothelial lipase (Kinnunen and Ehnolm 1976), and (3) apoC-III interaction with Apolipoprotein E (apoE), an important factor in liver reuptake of lipid particles by blocking apoE-mediated uptake of lipid particles in the liver (Breyer et al. 1999), and therefore, reducing apoC-III might enhance apoE-mediated uptake of lipid particles. Volanesorsen-mediated reduction of apoC-III could be contributing to one or all of these mechanisms resulting in the observed potent and sustained reductions in TG.

Through a novel apoC-III lowering mechanism of action, volanesorsen may provide the potential to manage triglyceride levels in FCS patients.

2.3 Volanesorsen

2.3.1 Mechanism of Action

Volanesorsen is a second-generation antisense oligonucleotide (ASO) drug targeted to human apoC-III. It is complementary to a region within the 3′ untranslated region of the apoC-III messenger ribonucleic acid (mRNA) and binds to the mRNA by Watson and Crick base pairing.

The hybridization (binding) of volanesorsen to the cognate mRNA, results in the RNase H1-mediated degradation of the apoC-III mRNA, thus preventing production of the apoC-III protein. Maximal antisense-mediated reduction of target mRNA levels is typically greater than 90% of control levels in sensitive tissues (Crooke and Bennett 1996; Zhang et al. 2010). Furthermore, reduction in target mRNA levels using this approach correlates directly with a subsequent reduction in target protein levels.

2.3.2 Chemistry

Chemically, volanesorsen is a synthetic oligomer of 20 nucleotides (i.e., a 20-mer) that are connected sequentially by phosphorothioate linkages. The nucleotide sequence of volanesorsen (Figure 2) is complementary to a 20-nucleotide stretch within the 3′ untranslated region of the apoC-III mRNA transcript at base position 489-508. Structurally, the oligonucleotide has 3 regions. Two (2) of them, the 5 nucleotides at the 5′ end and the 5 nucleotides at the 3′ end, are composed of 2′-*O*-(2-methoxyethyl) (MOE)-modified ribonucleotides. These MOE-modified nucleotides confer (1) increased affinity to the target mRNA (Altmann et al. 1996; McKay et al. 1999), (2) increased resistance to exonucleases and endonucleases (thereby increasing stability in tissue) (Geary et al. 2003), and (3) amelioration of some of the high dose toxicities thereby resulting in an improved safety profile compared to first generation antisense drugs containing phosphorothioate modified oligodeoxynucleotides (DNA) (Henry et al. 2000). The third region, the central portion of the oligonucleotide, is composed of 10 oligodeoxynucleotides. This chimeric design is called a MOE-Gapmer, and volanesorsen employs this chimeric structure to enable use of the RNase H1-mechanism for antisense activity. This is because while the 2′-MOE modification confers increased stability and affinity, it does not support RNase H1 catalysis of RNA hybridized to 2′-MOE-modified nucleotides (McKay et al. 1999). This is caused by conformational changes induced in the heteroduplex by 2′-alkoxy:RNA hybrids that are not recognized by RNase H1 enzymes (Inoue et al. 1987; Monia et al. 1993). By limiting the 2′-MOE modification to nucleotides flanking the phosphorothioate oligodeoxynucleotide core, the beneficial attributes of the 2′-MOE chemistry are preserved while also retaining RNase H1 recognition.

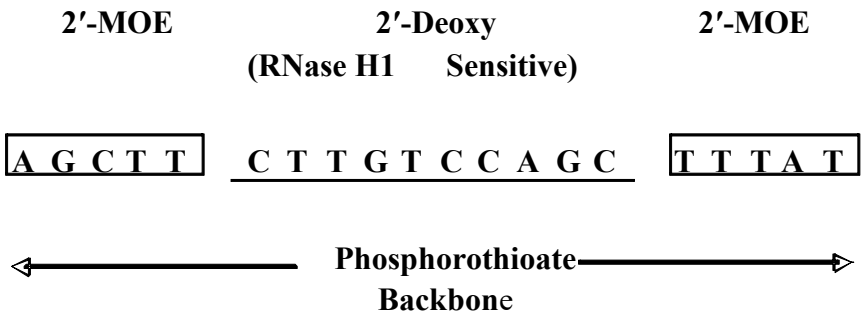


Figure 2 Design of Chimeric 2′-MOE Phosphorothioate Oligonucleotides (MOE-Gapmer). The sequence of volanesorsen is shown

2.3.3 Preclinical Experience

Inhibition of apoC-III using volanesorsen has been shown to potently reduce hepatic apoC-III mRNA as well as plasma apoC-III protein and TG in a dose- and time-dependent fashion in several species, including human apoC-III transgenic mice, and other rodent and monkey models. Treatment with volanesorsen also resulted in reduced VLDL and chylomicron TG and reduced postprandial TG in hypertriglyceridemic monkeys (Graham et al. 2013).

The pharmacokinetics (PK) and toxicity of volanesorsen have been assessed in mice, rats, and cynomolgus monkeys. General toxicity studies with volanesorsen for up to 39 weeks of treatment followed by up to a 20-week recovery period are complete. The preclinical toxicology program for volanesorsen consists of single dose safety pharmacology studies in the monkey (cardiovascular) and mouse (neurobehavioral and pulmonary assessment studies), *in vitro* and *in vivo* genetic toxicity assessment, repeat dose fertility and/or developmental reproductive toxicology studies in the mouse and rabbit and evaluation in the *in vitro* human Ether-á-go-go-related gene (hERG) assay.

Volanesorsen treatment-related findings in mice and monkeys were generally consistent with those expected for the 2′-MOE-class of ASOs. Treatment-related findings included effects consistent with drug accumulation in tissues in rodents and monkeys, species-dependent proinflammatory response in rodents and monkeys and complement activation and reductions in platelet counts in the monkey. In the mouse and monkey general toxicity studies, reduction of hepatic apoC-III mRNA (> 75%) was not associated with any findings that could be considered related to the pharmacologic inhibition of apoC-III for up to 39 weeks of treatment.

The long-term, chronic toxicology studies in rodents with volanesorsen produced a significant proinflammatory response that led to subsequent effects on the heart at high doses. The rodent species are most sensitive to the proinflammatory effects of antisense molecules. Importantly, these effects on the heart were not observed in the monkey chronic toxicity studies even at the highest doses tested where drug exposure was higher than that in rodents.

Because these changes were not observed in monkeys, the findings in the heart are considered to be rodent-specific and not relevant to humans. Nevertheless, such effects will be monitored by measurement of echocardiograms that will be included in this clinical study.

Volanesorsen caused no untoward effects in safety pharmacology studies (*in vitro* and *in vivo*) and was non-genotoxic (*in vitro* and *in vivo*). Volanesorsen had no effects on fertility or embryo/fetal development in the mouse or rabbit reproductive toxicity studies. In these studies, volanesorsen was detected in placental tissue but not in fetal tissue indicating that little, if any, drug was able to cross the placenta to reach the fetus. Reduction of apoC-III mRNA (64% in males and 47% in females) also did not affect fertility or cause untoward effects on embryo/fetal development in mice.

Detailed information concerning the preclinical studies conducted with volanesorsen can be found in the volanesorsen Investigator's Brochure.

2.3.4 Clinical Experience

Detailed information concerning the clinical studies conducted with volanesorsen can be found in the volanesorsen Investigator's Brochure. A summary is included below.

Volanesorsen has been evaluated in one Phase 1 study and two Phase 2 studies, all double blinded and placebo controlled. The total exposures comprise 99 patients and healthy volunteers administered volanesorsen from 50 to 400 mg subcutaneously up to 3 months (compared to 37 administered placebo).

All clinical trials of volanesorsen have shown large and clinically meaningful reductions in fasting plasma apoC-III and TG (~80% and 70%, respectively, mean reduction from baseline with 300 mg dose) with a very high degree of consistency of response between the different patient groups. This includes healthy volunteers, patients with moderate to severe hypertriglyceridemia not on background TG-lowering therapy, patients with moderate to severe hypertriglyceridemia on a background stable fibrate therapy (Gaudet et al. 2015), patients with FCS, and patients with T2DM.

In a Phase 2 study, 3 patients with FCS were treated with 300 mg/wk volanesorsen in an open-label fashion. These patients had a mean baseline fasting TG level of 1,844 mg/dL and all 3 patients achieved TG levels below or close to 500 mg/dL during the dosing period out to Day 92 (Figure 3). Two (2) of the FCS patients had an absolute reduction in fasting TG in excess of 1,500 mg/dL (Gaudet et al. 2014).

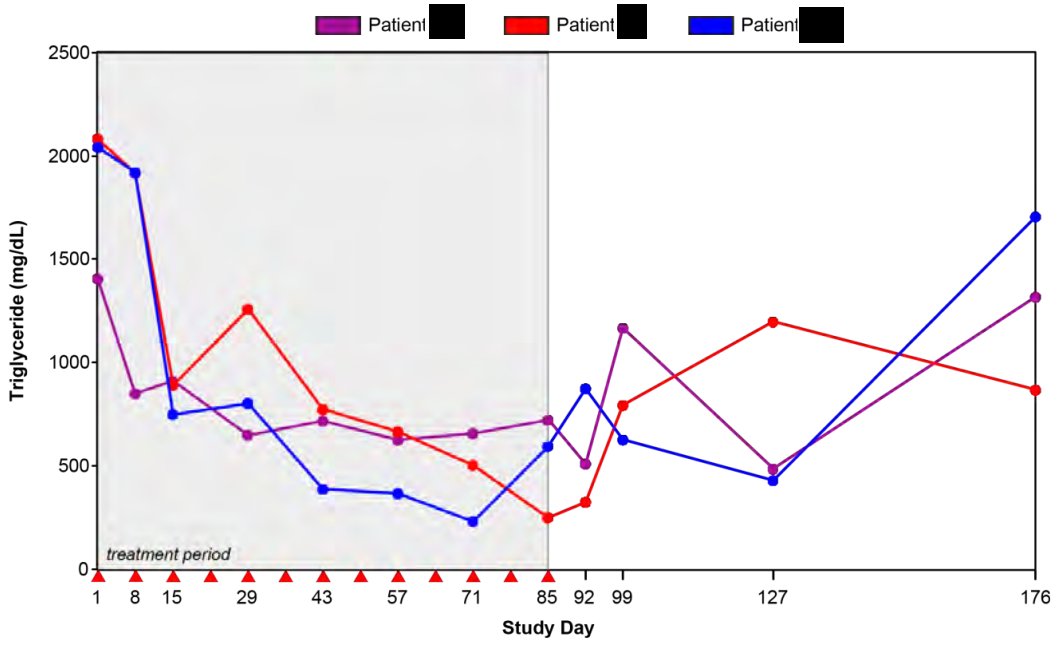


Figure 3 Fasting Triglycerides in Patients with FCS Treated with Volanesorsen

In clinical studies conducted to date volanesorsen has been well-tolerated and has shown a favorable safety profile. There has been no clinical or laboratory evidence of drug-drug interactions.

In the completed studies there have been no volanesorsen associated laboratory abnormalities suggestive of an effect on the renal (serum creatinine, proteinuria) or hepatic systems (alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin). In Phase 2 studies, there was a mild decrease of platelet count associated with volanesorsen administration that recovered in the post-treatment period and was not associated with platelet-related adverse events (AEs). In the blinded ongoing clinical trials of ISIS 304801, 2 patients of 142 dosed (as of February 29, 2016) had a decrease in platelet count to less than 50,000/mm^3 in the absence of major bleeding or clinically-relevant non-major bleeding and had Study Drug paused as per the monitoring and stopping rules for platelet counts (Section 8.6.3). Platelet counts recovered following suspension of dosing.

The most frequently observed AEs with volanesorsen were local reactions at the injection site. Local cutaneous reactions at the injection site defined as those events presenting as either pain, tenderness, erythema, pruritus or swelling occurring on the day of injection and persisting for at least 2 days were infrequent (~15% of injections), were almost always mild, resolved spontaneously, were non-progressive, and were not associated with systemic sequelae.

2.4 Rationale for Dose and Schedule of Administration

The dose and schedule selected for this study is 300 mg per week for 52 weeks. The dose of 300 mg per week is supported by both the cumulative nonclinical data available to date and the Phase 2 clinical data. In nonclinical studies, volanesorsen treatment-related effects in rodents and monkeys were consistent with drug accumulation in tissues and also include species-specific proinflammatory responses. In the monkey, the No-Observed-Adverse-Effect Level (NOAEL) was defined by the cumulative clinical pathology results and histopathology data which provide an adequate clinical margin. No nonclinical findings were considered to be related to the pharmacologic inhibition of apoC-III.

The safety data to date suggest that volanesorsen has been well-tolerated at dose levels up to 300 mg in patients with high triglycerides (including type 2 diabetes patients and administration in combination with fibrates and statins) with the most common AEs being local to the injection site and predominantly mild. A pooled analysis of safety for the Phase 2 studies did not demonstrate any clear difference in safety or tolerability between the different doses tested (100 mg, 200 mg, and 300 mg per week for 13 weeks).

Analysis of the cohorts in which volanesorsen was studied at different doses demonstrates dose-dependent pharmacology with respect to pharmacodynamic (PD) effect on the target, apoC-III, with a clear difference in the TG-lowering effect between the different doses in the 100 mg to 300 mg dose range as compared to placebo.

In addition to the nonclinical and clinical experience of volanesorsen, the dose and schedule of administration is supported by the preclinical and clinical safety experience of several other 2′-MOE-modified ASOs that have been safely administered intravenously and subcutaneously in multiple clinical studies at doses up to 1000 mg and for treatment durations that exceed 24 months (Santos et al. 2015).

3. EXPERIMENTAL PLAN

3.1 Study Design

This is an open-label study of:

Group 1: ISIS 304801-CS6 (index study) roll over FCS patients

Group 2: ISIS 304801-CS16 (index study) roll over FCS patients

Up to approximately 70 patients will receive 300 mg once weekly volanesorsen for 52 weeks.

Following the Week 52 visit, patients enter an at least 26-week post-treatment evaluation period or will participate in an expanded access program pending approval by the IRBs/IEC, and the appropriate regulatory authorities.

3.2 Number of Study Centers

This study will be conducted at multiple centers worldwide.

3.3 Number of Patients

Up to approximately 70 patients will be dosed.

3.4 Overall Study Duration and Follow-up

The Study will consist of the following periods:

3.4.1 Qualification

A qualification period of up to 2 weeks (unless approved by the Sponsor) is given to complete qualification assessments outlined in the Schedule of Procedures. Please refer to Section 4.1 and Appendix A.

3.4.2 Treatment

The treatment period is 52 weeks. Eligible patients will report to the Study Center for assessments at specified intervals throughout the 52-week treatment period as detailed in the Schedule of Procedures (Appendix A). During the treatment period, volanesorsen is administered by SC injection once weekly.

3.4.3 Post-Treatment

The post-treatment evaluation period is at least 26 weeks and consists of at least 6 Study Center visits on Weeks 54, 56, 58, 65, 71, and 78 (Weeks 54, 56, 58, and 71 may be conducted by a home healthcare nurse).

3.5 End-of-Study

The End-of-Study is last patient, last visit.

3.6 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will review (as needed) safety, tolerability and efficacy data collected on volanesorsen during this study. Based on its ongoing assessment of the safety and tolerability of volanesorsen, the DSMB will provide

recommendations to the Sponsor for modifying, stopping or continuing the study as planned. Details on the safety assessments, frequency of review and meeting schedules are outlined in the DSMB Charter and/or the statistical analysis plan (SAP).

4. PATIENT ENROLLMENT

4.1 Qualification

Before patients may be enrolled into the study, the Sponsor requires a copy of the Study Center's written independent ethics committee/institutional review board (IEC/IRB) approval of the protocol, informed consent form, and all other patient information.

Patients or their legally acceptable representatives must sign the consent form before any study-specific procedures or evaluations related to this open-label study are performed.

During the qualification period, the eligibility of the patient to enroll in the open-label study will be determined. Final assessments from the ISIS 304801-CS6 or ISIS 304801-CS16 studies may be used for qualification. A period of up to 2 weeks after completion of the ISIS 304801-CS6 or ISIS 304801-CS16 index studies (unless approved by the Sponsor) is given to complete qualification. Qualified patients will retain the unique patient identification number that was assigned to them during the ISIS 304801-CS6 or ISIS 304801-CS16 index studies. The patient identification number will be used to identify the patient throughout the extension trial and must be used on all study documentation related to that patient. The patient identification number must remain constant throughout the extension trial.

4.2 Enrollment

Patients will be enrolled into the treatment phase of the study after all qualification assessments have been completed and after the Investigator has verified that they are eligible per criteria in Sections 5.1 and 5.2. No patient may begin treatment prior to enrollment.

Eligible patients will be enrolled using an Interactive Voice/Web-Response System (IXRS).

5. PATIENT ELIGIBILITY

To be eligible to participate in this study candidates must meet the following eligibility criteria within 2 weeks of Study Day 1, or at the time point specified in the individual eligibility criterion listed.

5.1 Inclusion Criteria

1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law
2. Age ≥ 18 years at time of informed consent
3. Groups 1 and 2: Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement.

   Group 2: Patients who enrolled in ISIS 304801-CS16 must also meet the following criteria in order to enter into the open-label Study:

a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L)

b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) by documentation of the following:

- Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1)
- Post heparin plasma LPL activity of ≤ 20% of normal in medical history

c. Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 index study

4. Able and willing to participate in a 78-week study
5. Satisfy 1 of the following:

a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved), abstinent*, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration.

b. Males: Surgically sterile, abstinent* or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration.

* Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception

5.2 Exclusion Criteria

1. Diabetes mellitus with any of the following:

a. Newly diagnosed within 12 weeks of Qualification

b. HbA1c ≥ 9.0% at Qualification

c. Recent change in anti-diabetic pharmacotherapy (change in dosage or addition of new medication within 12 weeks of Qualification [with the exception of ± 10 units of insulin])

d. Anticipated need to change dose or type of medication during the treatment period of the Study (with the exception of ± 10 units of insulin)

e. Current use of GLP-1 agonists

2. Severe hypertriglyceridemia other than due to familial chylomicronemia syndrome
3. Active pancreatitis within 4 weeks prior to Qualification
4. History within 6 months of Qualification of acute or unstable cardiac ischemia (myocardial infarction, acute coronary syndrome, new onset angina), stroke, transient ischemic attack or unstable congestive cardiac failure requiring a change in medication or major surgery within 3 months of Qualification
5. Any of the following laboratory values at Qualification
   a. Hepatic:
      - Total bilirubin > upper limit of normal (ULN), unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL
      - ALT > 2.0 x ULN
      - AST > 2.0 x ULN
   b. Renal:
      - Persistently positive (2 out of 3 consecutive tests ≥ 1+) for protein on urine dipstick. In the event of a positive test eligibility may be confirmed by a quantitative total urine protein measurement of < 500 mg/24 hrs
      - Persistently positive (2 out of 3 consecutive tests ≥ trace positive) for blood on urine dipstick. In the event of a positive test eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field
      - Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault < 50 mL/min (MDRD or CKD-EPI formulas can be used instead of Cockcroft-Gault for estimation of GFR in patients with low body weight after discussion with Sponsor Medical Monitor)
   c. Cardiac Troponin I > ULN at Qualification
   d. LDL-C > 130 mg/dL at Qualification
   e. Any other laboratory abnormalities which, in the opinion of the Investigator or the Sponsor, would make the patient unsuitable for inclusion
6. Uncontrolled hypertension (BP > 160/100 mm Hg)
7. History of thrombocytopenia (platelet count < 100,000/mm^3) or bleeding diathesis or coagulopathy or clinically-significant abnormality in coagulation parameters at Qualification
8. History of heart failure with NYHA greater than Class II
9. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1

10. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B
11. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated
12. Treatment with another investigational drug, biological agent, or device within 1 month of Qualification, or 5 half-lives of investigational agent, whichever is longer
13. Unwilling to comply with lifestyle requirements (Section 6.3)
14. Use of any of the following:
    a. Statins, omega-3 fatty acids (prescription and OTC), or fibrates unless on a stable dose for at least 3 months prior to Qualification and dose and regimen expected to remain constant during the treatment period. Patients taking OTC omega-3 fatty acids should make every effort to remain on the same brand throughout the study
    b. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to Qualification
    c. Systemic corticosteroids or anabolic steroids within 6 weeks prior to Qualification unless approved by the Sponsor Medical Monitor
    d. Atypical antipsychotic medications (e.g., olanzapine and clozapine) unless on a stable dose for at least 3 months prior to Qualification and dose and regimen expected to remain stable throughout the study
    e. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to Qualification and dose and regimen expected to remain constant during the treatment period
    f. Glybera gene therapy within 2 years prior to Qualification
    g. Oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, and apixaban) unless on a stable dose for at least 4 weeks prior to Qualification and regular clinical monitoring is performed
    h. Tamoxifen, estrogens or progestins unless on a stable dose for at least 4 months prior to Qualification and dose and regimen expected to remain constant during the treatment period
    i. Plasma apheresis within 4 weeks prior to Qualification or planned during the study
    j. Prior exposure to ISIS 304801
    k. Any other medication unless stable at least 4 weeks prior to Qualification (Occasional or intermittent use of over-the-counter medications will be allowed at Investigator's discretion)
15. Blood donation of 50 to 499 mL within 30 days of Qualification or of > 499 mL within 60 days of Qualification
16. Known hypersensitivity to any of the excipients of the Study Drug (ISIS 304801 or placebo)

17. Have any other conditions, including new or worsening of existing condition, which, in the opinion of the Investigator or the Sponsor would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the study

6. STUDY PROCEDURES

6.1 Study Schedule

All required study procedures are outlined in Appendices A, B, C, and D.

6.1.1 Qualification

Please refer to Section 4.1 and Appendix A.

6.1.2 Treatment Period

The patients, Investigators, study staff, and the Sponsor will remain blinded to lipid data through the last patient's Week 13 visit of the open-label study or until results from the database locks for the ISIS 304801-CS6 and ISIS 304801-CS16 index studies become available, whichever comes first.

During the treatment period, patients will report to the study center for clinic visits a minimum of 5 times during Weeks 1-52 (see Schedule of Procedures in Appendix A). Study Drug will be administered once weekly (Section 8.1). Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), AEs, concomitant medication/procedure information, lipid panel, volanesorsen plasma concentrations, immunogenicity (IM) testing, liver/spleen MRI, ECGs, echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Adverse events at the injection site should be collected as adverse events. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period and all patients will complete a daily food diary for one week prior to their quarterly visit. All blood and urine samples should be collected prior to volanesorsen administration. Blood sampling at Weeks 2.5, 4, 6, 8, 10, 12, 15, 17, 19, 21, 23, 25, 28, 30, 32, 34, 36, 40, 42, 44, 46, 48, and 50 may be conducted by a home healthcare nurse. Approval for study procedures to be conducted by a home healthcare nurse on other outpatient visit days will require prior approval by the Sponsor. Patients must be fasted prior to drawing all blood samples and samples drawn locally should also be sent to the central laboratory for analysis whenever possible. Every effort should be made to ensure the previous week's dose is given 7 days prior to a scheduled clinic visit. Dosing instructions and training will be provided to the patient where applicable.

All reasonable attempts should be made to ensure compliance with the visit schedule as outlined in Appendix A. However, in the event that a visit does not occur or is delayed, all subsequent visits should be calculated based on the time elapsed since Day 1 rather than from the date of the previous visit.

6.1.3 Pharmacokinetic (PK) Subgroup

A subgroup of patients will participate in an extended PK collection. Patients in this subgroup will have more frequent PK sampling over a 24-hour period following the first dose on Study Day 1 in order to evaluate the plasma PK parameters of volanesorsen. Patients in this

subgroup will have an additional visit to the clinic, or by a home healthcare nurse, on Day 2 to collect a 24-hour post-dose blood draw after dosing on Day 1. The detailed PK sampling schedules are outlined in Appendix C.

Participation in the PK subgroup is optional for sites and patients, and consent may be withdrawn for the subgroup-specific procedures (e.g., multiple blood draws for PK) without being withdrawn from the study. If a patient withdraws consent from the subgroup procedures, he/she should remain on study and continue to follow all the non-subgroup assessments and procedures as outlined in Appendix A.

6.1.4 Post-Treatment Period

After completion of the Week 52 visit assessments, patients will enter the at least 26-week post-treatment evaluation period or will participate in an expanded access program pending approval by the IRBs/IEC, and the appropriate regulatory authorities. The 26-week period consists of at least 6 Study Center visits on Weeks 54, 56, 58, 65, 71, and 78 (Weeks 54, 56, 58, and 71 may be conducted by a home healthcare nurse), as outlined in the Schedule of Procedures in Appendix A.

6.2 Additional Study Assessments

6.2.1 Laboratory Assessments

Laboratory analyte samples will be collected throughout the study. A list of these analytes is contained in Appendix B.

Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1 week and determined not to have met a stopping rule before dosing can continue.

If there is no reportable platelet count within 14 days of the last platelet count, the Investigator will contact the patient to hold dosing until a new platelet count is obtained and reviewed.

All platelet count results will be promptly reviewed by the Investigator to ensure that the count has not met the stopping rule and to determine whether the rate of decline is suggestive that the patient could be approaching the dose pause rule of 75,000/mm^3.

Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor.

6.2.2 Physical Exams and Vital Signs

Physical exams and vital signs will be performed as indicated in the Schedule of Procedures (Appendix A). Vital signs should include weight, blood pressure, pulse rate, respiratory rate and body temperature. Blood pressure and pulse rate will be recorded after the patient has been in a sitting position for at least 5 minutes. Semi-supine systolic and diastolic blood pressure should always be measured on the same arm (preferentially on the left arm). Height will be measured at the Day 1 visit.

6.2.2.1 Eruptive Xanthoma

At each visit, patients will be asked whether they have had any episodes of eruptive xanthoma since their last visit and the number/duration of the events will be recorded. Physical exams should also include skin examination for presence/resolution of eruptive xanthomas. If a patient experiences an episode of eruptive xanthoma during the study, photos of the area should be taken, if possible.

6.2.2.2 Lipemia Retinalis

If possible, lipemia retinalis will be assessed by fundus photography prior to administration of the first dose of Study Drug (for ISIS 304801-CS16 roll over patients) and repeated at Week 52. Images will be evaluated by an independent assessor, blinded to the patient's treatment assignment.

6.2.3 Echocardiography

Echocardiography for assessment of left and right ventricular function and mitral and aortic valve function will be conducted at Week 26 and Week 52 in all patients. For the purpose of assessment of treatment-emergent changes, all echocardiograms will be evaluated on an ongoing basis by an independent central reader. Results will be provided to the DSMB for their review.

6.2.4 ECG

The ECG will be recorded after the patient has been resting in a supine position for at least 5 minutes. ECGs will be performed in triplicate at Week 13, Week 26, Week 38, Week 52, Week 65, and Week 78.

6.2.5 MRI

MRI of the liver and spleen will be conducted at Week 52 for all patients for whom MRI is not contraindicated, e.g., patients having metal implants.

MRIs will be conducted using standardized procedures and settings. MRIs will be read by an independent central reader to assess liver fat and liver and spleen size**.**

6.2.6 Quality of Life Assessments

All patients will complete Quality of Life Questionnaires (EQ-5D and SF-36) at Week 1, Week 13, Week 26, Week 52, Week 65, and Week 78.

6.2.7 Disease Symptom Diary

All patients will complete a symptom questionnaire once a week starting at the beginning of the qualification period and continuing to the end of the post-treatment follow-up period.

6.2.8 Diet Monitoring

The diets of patients enrolled in the study will be monitored as follows:

1. All patients will be required to maintain a 7-day food diary prior to Week 1, Week 13, Week 26, Week 52, Week 65, and Week 78.

2. Patients will receive diet/alcohol counseling by qualified study personnel at clinic visits throughout the course of the study. Qualified study personnel will telephone the patient to provide diet/alcohol counseling for visits that are conducted by a clinical service.
3. In addition to the 7-day food diary and the diet /alcohol counseling during clinic visits, telephone calls from a dietitian or qualified study personnel to assess as to how each patient is maintaining their diet will be conducted randomly during the treatment and post treatment follow-up periods.

6.2.9 Family History

Family history of hypertriglyceridemia and pancreatitis will be collected for each patient.

6.3 Restriction on the Lifestyle of Patients

6.3.1 Contraception Requirements

All male patients and women of childbearing potential must refrain from sperm/egg donation and either be abstinent† or, if engaged in sexual relations of child-bearing potential, practice effective contraception from the time of signing the informed consent form until at least 13 weeks after their last dose of study treatment.

Male patients must also encourage their female partner to use effective contraception from the time of signing the informed consent until 13 weeks after the subject's last dose of study treatment.

For the purposes of this Study, women of childbearing potential are defined as any female who has experienced menarche, and who does not meet 1 of the following conditions:

- Postmenopausal: 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved
- 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Post hysterectomy

For the purposes of the study, effective contraception is defined as follows:

For male patients:

- Effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the use of condoms together with spermicidal foam/gel/film/ cream/suppository. Male patients must also encourage their female partner to use effective contraception from the time of signing the informed consent until 3 months after the patient's last dose of study treatment. Effective contraceptive for the female partner includes: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or barrier methods (female condom*, diaphragm, sponge, cervical cap) together with spermicidal foam/gel/film/cream/suppository. Male patients with partners that are pregnant must use condoms to ensure that the fetus is not exposed to the Study Drug.

For female patients:

- Using 1 or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or any 2 barrier methods (a combination of male or female condom* with diaphragm, sponge, or cervical cap) together with spermicidal foam/gel/film/cream/suppository.

* Note: A female condom and a male condom should not be used together as friction between the two can result in either product failing.

† Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception

6.3.2 Other Requirements

All patients will be required to fast for at least 10 hours and preferably not more than 12 hours before visits requiring fasted blood sampling.

All patients will be encouraged to follow a diet comprising ≤ 20 g fat per day during the study.

Alcohol should not be consumed during the study.

All patients will be given an instruction card that must be presented to the treating physician if a suspected case of pancreatitis occurs. The card will explain that the patient is in a clinical trial and that serum lipase and/or amylase measures should be done in order to adjudicate the event, based on Atlanta Classification (Banks et al. 2013). If serum or amylase activity is less than 3 x upper limit of normal (ULN), imaging, preferably contrast-enhanced computed tomography, should be considered to confirm the diagnosis of acute pancreatitis per the Atlanta Criteria.

7. STUDY DRUG

7.1 Volanesorsen Description

Volanesorsen drug product (ISIS 304801) characteristics are listed in Table 1.

Volanesorsen (ISIS 304801) is contained in glass prefilled syringes (PFS). Volanesorsen and its storage and preparation instructions will be provided by the Sponsor or designee. Volanesorsen must be stored securely at 2 °C to 8 °C and be protected from light.

Table 1 Volanesorsen (ISIS 304801) Characteristics

Strength	200 mg/mL
Volume/Formulation	1.5 mL solution per PFS
Dose	300 mg once weekly
Route of Administration	SC

7.2 Packaging and Labeling

The Sponsor will provide the Investigator with packaged volanesorsen labeled (ISIS 304801) in accordance with specific country regulatory requirements.

7.3 Study Drug Accountability

The study staff is required to document the receipt, dispensing, and return/destruction of volanesorsen provided by the Sponsor. The Study Center must return all unused volanesorsen to the Sponsor or designee. All used syringes must be disposed of as per the site's hazardous waste destruction policy.

8. TREATMENT OF PATIENTS

8.1 Volanesorsen Administration

For each individual patient, volanesorsen will be administered subcutaneously as a single 1.5 mL 300 mg injection once weekly for Weeks 1-52. Patients entering this ISIS 304801-CS7 study on a reduced dose or dose frequency of Study Drug (volanesorsen), for safety or tolerability reasons in their index study (ISIS 304801-CS6 or ISIS 304801-CS16), will receive a reduced dose or dose frequency of volanesorsen for continued safety or tolerability as outlined in Sections 8.5 and 8.6. Patients entering this CS7 study having dose or dose frequency reduced in the CS16 index study after 13 weeks of treatment, as outlined in CS16 Amendment 4 Section 8.7, can receive the 300 mg once weekly dose of volanesorsen.

Patients should receive 1 dose per week, with weeks always defined relative to Study Day 1. For example if a patient receives the first dose on a Monday, subsequent doses should be given on Mondays, if possible. If a patient misses an injection, or if dosing on the usual day is not possible, the patient can reschedule the injection provided that 2 doses are administered at least 2 days apart.

Every effort should be made to ensure the previous week's dose is given 7 days prior to a scheduled clinic visit.

Please refer to the Study Drug Manual provided by the Sponsor for more detailed instructions for volanesorsen preparation and administration.

8.2 Other Protocol-Required Drugs

There are no other protocol-required drugs (Section 6.2.5).

8.3 Other Protocol-Required Treatment Procedures

There are no other protocol required treatment procedures for this study.

8.4 Treatment Precautions

There are no specific treatment precautions required for this study.

8.5 Safety Monitoring Rules

Please refer also to the 'Guidance for Investigator' section of the Investigator's Brochure.

For the purposes of safety monitoring baseline is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 (e.g., qualification assessments or assessments from the final visits of ISIS 304801-CS6 and ISIS 304801-CS16 index studies if used for qualification).

In addition to the standard monitoring of clinical safety parameters, the following guidelines are provided for the monitoring of selected parameters chosen based on preclinical and clinical observations.

Confirmation Guidance: At any time during the study (Treatment or Post-Treatment Periods), the initial clinical laboratory results meeting the safety monitoring or stopping criteria presented below **must be confirmed** by performing measurements (ideally in the same laboratory that performed the initial measurement) on new specimens. All new specimen collections should take place as soon as possible (ideally within 3 days of the initial collection). For stopping rules, if the initial laboratory result is observed during the Treatment Period, the results from the retest **must be available** prior to administering the next dose of volanesorsen.

In addition to the safety monitoring parameters listed below, the Sponsor may request confirmation of additional lab values.

Re-dosing Guidance: Patients with initial laboratory test values that reach a stopping rule must not be re-dosed until the re-test results are available. In general, patients who do not meet the stopping rules based upon retest may continue dosing. However, the Investigator and the Sponsor Medical Monitor (or appropriately qualified designee) should confer as to whether additional close monitoring of the patient is appropriate. Reduction in dose or dose frequency may also be initiated as noted in Section 8.7. If any of the stopping criteria described below (refer to Sections 8.6.1 to 8.6.3) are met, the patient will be dose paused or permanently discontinued (as described in the stopping criterion concerned) from further treatment with volanesorsen, and evaluated fully as outlined below and in consultation with the Sponsor Medical Monitor or appropriately qualified designee, and will be followed up in accordance with Section 8.8 of the protocol.

8.5.1 Safety Monitoring for Liver Chemistry Tests

The following rules are adapted from the draft guidance for industry, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," issued by the U.S. Department of Health and Human Services, Food and Drug Administration, July 2009. For a definition of Baseline please refer to guidance in Section 8.5 above.

In the event of an ALT or AST measurement that is > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) at any time during the study (Treatment or Post-Treatment Period), the initial measurement(s) should be confirmed as described above. Additional confirmatory measurements should also be performed if ALT or AST levels increase to 5 x ULN.

Frequency of Repeat Measurements: Patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) should have their liver chemistry tests (ALT, AST, alkaline phosphatase (ALP), international normalized ratio (INR) and total bilirubin) retested at least once-weekly until ALT and AST levels become ≤ 1.2 x ULN or 1.2 x baseline value if the baseline value was > ULN.

Further Investigation into Liver Chemistry Elevations: For patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), the following evaluations should be performed:

1. Obtain a more detailed history of symptoms and prior and concurrent diseases
2. Obtain further history for concomitant drug use (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
3. Obtain a history for exposure to environmental chemical agents and travel
4. Serology for viral hepatitis (HAV IgM, HBsAg, HCV antibody, CMV IgM, and EBV antibody panel)
5. Serology for autoimmune hepatitis (e.g., antinuclear antibody [ANA])

Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic CT or MRI scans, may be performed at the discretion of the Investigator, in consultation with the Sponsor Medical Monitor. Repetition of the above evaluations should be considered if a patient's ALT and/or AST levels reach 5 x ULN.

8.5.2 Safety Monitoring for Platelet Count Results

Actions to be taken in the event of reduced platelet count are shown in Table 2 in Section 8.6.3.

Additional lab tests will be determined by the Sponsor Medical Monitor or designee in consultation with the Investigator.

Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor (See also Stopping Rules Section 8.6.3).

8.5.3 Safety Monitoring for Minor Bleeding Events

Minor bleeding events are those that do not fulfill the criteria for major bleeding or clinically-relevant, non-major bleeding events (which are defined in Section 8.6.3), for example excess bruising, petechiae, gingival bleeding on brushing teeth. If a minor bleeding event occurs, the Investigator must notify the Sponsor Medical Monitor and additional testing of coagulation parameters activated partial thromboplastin time (aPTT), prothrombin time (PT), INR and platelet count should be performed.

8.5.4 Safety Monitoring for Constitutional Symptoms

Patients will be instructed to promptly report any signs of symptoms of fever or constitutional symptoms that may arise during the study and the Investigator should closely evaluate all potential causes, including concomitant illness. Patients that experience persistent constitutional

symptoms should be discussed with the Sponsor Medical Monitor or designee to determine whether additional monitoring or laboratory tests are required.

8.5.5 Safety Monitoring for LDL-C Elevations

Beginning at Week 13, laboratory alerts will be in place to notify the Investigator if a patient has a low-density lipoprotein-cholesterol (LDL-C) > 160 mg/dL (> 130 mg/dL for patients with T2DM) on 2 consecutive visits. If this occurs, LDL-C values for this patient will be unblinded for the remainder of the study and the Investigator will be encouraged to initiate/adjust treatment to lower LDL-C according to country-specific guidelines (e.g., initiate statin therapy or increase the statin dose for patients who are already on treatment).

8.5.6 Safety Monitoring for Insulin, Oral Antidiabetic Medication and Glucose

All patients on insulin will monitor their glucose levels with a glucometer as per standard practice guidelines and bring their glucometer or glucometer log printout to every clinic visit. In addition, patients who are not on insulin but use a glucometer should also bring their glucometer and/or glucometer log printout to every clinic visit.

- The Investigator or delegate will review the glucometer reading or printout at every clinic visit to evaluate if fasting pre-breakfast self-monitored plasma glucose values exceed threshold values as per the Safety Monitoring Rules for Hyperglycemia below.

All diabetic patients will note any changes in their insulin dose and /or oral antidiabetic therapy, as well as any hypoglycemic episode they may experience.

- The Investigator or delegate will ask patients at every clinic visit if they made changes in their insulin dose or oral antidiabetic therapy, and if they experienced a hypoglycemic episode.
    - Patients will be instructed on the monitoring and management of hypoglycemic episodes at each visit.
    - Documented symptomatic hypoglycemic episodes should be captured as adverse events in the adverse event CRF. Documented symptomatic hypoglycemia is defined as typical hypoglycemia symptoms accompanied by measured plasma glucose ≤ 70 mg/dL (≤ 3.9 mmol/L).
    - Any changes in insulin dose or oral antidiabetic therapy should be captured into the Concomitant Medication CRF.

8.5.7 Safety Monitoring for Documented Severe Hypoglycemia

A **documented severe hypoglycemic event** is defined as one in which the patient requires assistance of another person to obtain treatment for the event and has a plasma glucose level ≤ 70 mg/dL (≤ 3.9 mmol/L). The rescue treatment of hypoglycemia may include IV glucose or buccal or intramuscular glucagon.

The definition of severe symptomatic hypoglycemia includes all episodes in which neurological impairment was severe enough to prevent self-treatment and which were thus thought to place patients at risk for injury to themselves or others. Note that “requires assistance” means that the

patient could not help himself or herself. Someone being kind that assists spontaneously the patient when not necessary does not qualify as "requires assistance."

Severe hypoglycemia will be qualified as a SAE only if it fulfills SAE criteria.

If a patient presents with symptoms of hypoglycemia, the Investigator will need to take immediate action to confirm the patient's glucose level and treat the patient accordingly.

The experience of hypoglycemia may vary greatly from patient to patient. However, there are certain classical signs and symptoms, of which patients should be aware as a clue that their blood glucose may be low. Common symptoms include headache, heart pounding, confusion, disorientation, numbness or tingling, pale skin, shakiness or tremulousness, increased appetite, anxiousness or nervousness, lightheadedness or dizziness, sweating, and weakness. Coma could occur if blood sugar correction is not performed.

If patients suspect they might be having a hypoglycemia reaction, they should check their blood glucose using their meters as soon as possible, before treatment if possible, provided they feel it is safe to do so. If there is doubt about safety they should treat the event first, using some sugar, milk, or juice for example, then obtain and record a blood glucose value as soon as possible thereafter. The time and nature of treatment should be noted, and especially if any blood glucose result was before or after treatment. It would be helpful for the patient to note if a contributory factor (e.g., missed or reduced meals, unaccustomed physical activity) occurred earlier in the day of the event.

8.5.8 Safety Monitoring for Hyperglycemia

Upward dose titration and/or addition of any other anti-hyperglycemic agent(s) will not be allowed during the course of the study, unless specific threshold values are met at Week 13 or later and confirmed on subsequent testing (ideally within 1 week of the initial test).

HbA1c is monitored every 3 months throughout the study. In addition, patients on insulin should self-monitor their plasma glucose (SMPG) routinely on a glucometer as per practice guidelines. If a fasting pre-breakfast SMPG value exceeds the specific glycemic limit, the patient should check it again on the following 2 days. If all the fasting pre-breakfast values on 3 consecutive days exceed the specific limit, the patient should contact the Investigator and an unscheduled central laboratory FPG measurement and HbA1c should be performed.

The threshold values are defined as:

- FPG > 270 mg/dL (15.0 mmol/L)
- HbA1c > 9% (for patients with baseline HbA1c < 8% and HbA1c increase of more than 1% from baseline (for patients with baseline HbA1c ≥ 8 and < 9%)

In case of confirmed FPG/HbA1c above the threshold value, the Investigator should ensure that no reasonable explanation exists for insufficient glucose control and in particular that:

- Plasma glucose was actually measured in the fasting condition (i.e., after at least 10 hours fast)

- Absence of intercurrent disease which may jeopardize glycemic control. In case of an emergency (e.g., surgery, infection), the Investigator can take appropriate measures for glycemic control
- Compliance to treatment is appropriate
- Compliance to diet and lifestyle is appropriate

If any of the above can reasonably explain the insufficient glycemic control, the Investigator should consider the following:

- Investigation and treatment of intercurrent disease (to be reported in adverse event (AE)/concomitant medication parts of the e-CRF)
- Stress on the absolute need to be compliant to treatment
- Organize a specific interview with a Registered Dietician or other qualified nutrition professional and stress on the absolute need to be compliant to diet and lifestyle recommendations

A FPG/HbA1c follow-up assessment should be arranged after appropriate action has been taken. If none from the above-mentioned reasons can be found, or if appropriate action fails to decrease FPG/HbA1c under the threshold values, additional medication may be introduced at the Investigator's discretion and according to local guidelines after discussion with the Sponsor Medical Monitor.

8.5.9 Acute Pancreatitis

If a patient has an episode of acute pancreatitis, dosing with Study Drug should be suspended temporarily until the patient is clinically stable. The suitability of the patient for continued dosing and the need for any modification to treatment schedule (refer to Section 8.7) will be determined by the Investigator in consultation with the Study Medical Monitor.

8.6 Stopping Rules

For the purposes of stopping rules baseline is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1.

8.6.1 Stopping Rules for Liver Chemistry Elevations

In the event of laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor,** dosing of a patient with volanesorsen will be stopped permanently; values that are not confirmed due to failure to retest or missing lab values will be presumed confirmed:

1. ALT or AST > 8 x ULN, which is confirmed
2. ALT or AST > 5 x ULN, which is confirmed and persists for ≥ 2 weeks
3. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed **and** total bilirubin > 2 x ULN or INR > 1.5

4. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed, and the new appearance (i.e., onset coincides with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> ULN) felt by the Investigator to be potentially related to hepatic inflammation

8.6.2 Stopping Rules for Renal Function Test Results

In the event of a persistent elevation that is observed over 2 consecutive weeks, for any of the 3 criteria below, dosing of a patient with volanesorsen may be stopped temporarily:

1. Serum creatinine increase that fulfill all of the following criteria: ≥ 0.3 mg/dL (26.5 µmol/L) and ≥ 40% above baseline creatinine values and > ULN
2. Proteinuria, dipstick 2 + (confirmed by dipstick retest and then further confirmed by a quantitative total urine protein measurement of > 1.0 g/24 hour)
3. Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault ≤ 40 mL/min that is confirmed by a 24-hour urine collection

The possible dosing re-initiation or follow-up schedule for any events meeting either of these criteria will be determined by the Investigator **in consultation with** the Sponsor Medical Monitor or designee.

8.6.3 Stopping Rules for Platelet Count Results

Actions to be taken in the event of a low platelet count are summarized in Table 2 below.

In the event of a platelet count less than 75,000/mm^3 that is associated with major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with volanesorsen will be stopped permanently. The follow-up schedule for any events meeting this stopping criterion will be determined by the Investigator in consultation with the Sponsor Medical Monitor.

In the event of any platelet count less than 50,000/mm^3, or a rate of decline ≥ 50% between two consecutive assessments, irrespective of the platelet level, then dosing of a patient with volanesorsen will be stopped permanently. Platelet count will be monitored daily until 2 successive values show improvement then monitored every 2-3 days until platelet count is stable.

Administration of steroids is recommended for patients whose platelet count is less than 25,000/mm^3. Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (**note:** may require continuation with oral steroids after methylprednisolone). In order to reduce the unlikely but potential increased risk of pancreatitis during the period of corticosteroid therapy, triglyceride levels will be monitored weekly during corticosteroid treatment and the laboratory alert will be changed from an increase of 2,000 to 500 mg/dL during that period.

In the event of a platelet count less than 75,000/mm^3, and in the absence of major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with volanesorsen should be suspended temporarily until the platelet count has recovered to> 100,000/mm^3. If dosing is continued it should be at a reduced dose frequency of 300 mg every 2 weeks or a reduced dose of 150 mg per week (refer to Section 8.7). The suitability of the patient for continued dosing will be determined by the Investigator in consultation with the Study Medical Monitor and will be based on factors such as the original rate of decline in the patient's platelet count, whether any bleeding events were experienced by the patient, and the speed of recovery of platelet count upon holding of dosing.

If after the first dosing rechallenge the platelet count again falls below 75,000/mm^3, then dosing of the patient with Study Drug will be stopped permanently.

Following a rechallenge platelet count should be tested every week until count is stable.

Any unreportable platelet count result must be rechecked and determined not to have met a stopping rule before dosing can continue.

If there is no reportable platelet count within 14 days of the last platelet count, the Investigator will contact the patient to hold dosing until a new platelet count is obtained and reviewed.

Definition of Major Bleeding Events (Schulman et al. 2005):

- Fatal bleeding, and/or
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarterial or pericardial, or intramuscular with compartment syndrome, and/or
- Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more within 24 hours, or leading to transfusion of 2 or more units of whole or red cells

Definition of Clinically-Relevant, Non-Major Bleeding Events (Schulman et al. 2005):

1. Multiple-source bleeding
2. Spontaneous hematoma > 25 cm^2
3. Excessive wound hematoma (not injection site related)
4. Macroscopic hematuria (spontaneous or lasting > 24 hours if associated with an intervention)
5. Spontaneous rectal bleeding; epitasis, gingival bleeding, hemoptysis, hematemesis
6. Bleeding after venipuncture for > 5 minutes

Table 2 Actions in Patients with Low Platelet Count

Platelet Count on Rx	Drug Dose	Monitoring
Normal range, > 140K/mm^3	No action	Monitor every 2 weeks
100K-140K/mm^3	No action	Closer observation Monitor every 1 week until stable*
75K-100K/mm^3	Permanently reduce dose frequency to 300 mg every 2 weeks or reduce dose to 150 mg weekly	Closer observation Monitor every 1 week
50K-75K/mm^3	If occurs while on dose of 300 mg every 2 weeks or 150 mg every week then permanently discontinue Study Drug, otherwise dose pause. When platelet count returns to > 100K/mm^3 restart dosing at dose frequency of 300 mg every 2 weeks or 150 mg weekly **only if approved by Sponsor Medical Monitor**	Closer observation Monitor every 2-3 days until 2 successive values show improvement Consider discontinuation of antiplatelet agents/NSAIDS/ anticoagulant medication
25K-50K/mm^3 or a rate of decline ≥ 50% between two consecutive assessments, irrespective of the platelet level	Permanently discontinue Study Drug	Closer observation Monitor daily until 2 successive values show improvement then monitor every 2-3 days until platelet count stable Discontinue antiplatelet agents/NSAIDS/anticoagulant medication while platelet count < 50K/mm^3 if possible
< 25K/mm^3	Permanently discontinue Study Drug	Closer observation: Monitor daily until 2 successive values show improvement then monitor every 2-3 days until platelet count stable Steroids recommended** Consider need for hospitalization and referral to hematologist Discontinue antiplatelet agents/NSAIDS/anticoagulant medication while platelet count < 50K/mm^3 if possible

* At least 3 consecutive values measured weekly that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3

** Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (**note**: may require continuation with oral steroids after methyl prednisolone). In order to reduce the unlikely but potential increased risk of pancreatitis during the period of corticosteroid therapy, triglyceride levels will be monitored weekly during corticosteroid treatment and the laboratory alert will be changed from an increase of 2,000 to 500 mg/dL during that period.

8.7 Adjustment of Dose Frequency

Dose adjustments for platelet count reduction must be made in accordance with Section 8.6.3 and Table 2 (above).

Other dose adjustments, including dose interruptions, and/or decreasing the dose or dose frequency will be allowed for safety and tolerability. Any proposed adjustment to treatment schedule must be discussed with, and approved by, the Study Medical Monitor prior to initiation. Up to 2 adjustments in the treatment schedule may be allowed.

Patients may be dose paused in response to AEs after consultation with Study Medical Monitor.

8.8 Discontinuation of Study Treatment

A patient must permanently discontinue study treatment for any of the following:

- The patient becomes pregnant. Report the pregnancy according to instructions in Section 9.5.4
- The patient withdraws consent
- The patient experiences an AE that necessitates permanent discontinuation of study treatment
- The patient develops laboratory test abnormalities that meet any of the stopping rules listed in Section 8.6

The reason for discontinuation of study treatment must be recorded in the CRF and source documentation.

8.8.1 Follow-up Visits for Early Termination from Treatment Period

Any patient who discontinues early from the Treatment Period should be followed as per the platelet monitoring rules shown in Table 2 in Section 8.6.3 for the first 6 weeks after discontinuing Study Drug. Following this period, if the platelet count is stable (at least 3 consecutive values that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3), the next platelet count should be taken within at least 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug. Patients should also be strongly encouraged to attend applicable landmark visits at Weeks 12, 13, 25, 26, and 50, 52 (calculated based on the time elapsed since Day 1) to collect fasting lipid panels and conduct safety assessments in accordance with the Schedule of Procedures in Appendix A. Any patient who discontinues treatment after Week 44 should also be strongly encouraged to attend a final follow-up visit (Week 78 visit assessments) approximately 26 weeks after their last dose of Study Drug, in addition to the applicable landmark visits.

If the patient declines or is unable to participate in the above, an early termination (ET) visit (Week 52 visit assessments) should be performed at the time of withdrawal, at a minimum, and ideally within 2 weeks from the last dose of Study Drug.

8.8.2 Follow-up Visits for Early Termination from Post-Treatment Follow-up Period

The patient who requests to withdraw from the study during the Post-Treatment Follow-up Period should be encouraged to follow the platelet monitoring rules shown in Table 2 in Section 8.6.3 for the first 6 weeks after discontinuing Study Drug. Following this period, if the platelet count is stable (at least 3 consecutive values that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3), the next platelet count should be taken within at least

6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug. Patients should also be encouraged to undergo a final follow-up visit (Week 78, see Appendix A) prior to leaving the study.

If a patient withdraws due to an AE at any time during the study, the Investigator should arrange for the patient to have appropriate follow-up until the AE has resolved or stabilized.

8.9 Withdrawal of Patients from the Study

Patients must be withdrawn from the study for any of the following:

- Withdrawal of consent
- The patient is unwilling or unable to comply with the protocol

Other reasons for withdrawal of patients from the study might include:

- At the discretion of the Investigator for medical reasons
- At the discretion of the Investigator or Sponsor for noncompliance
- Significant protocol deviation

All efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information, including the reason for withdrawal from study, must be recorded in the CRF.

Any patient who withdraws consent to participate in the study will be removed from further treatment and study observation immediately upon the date of request. These patients should be encouraged to complete the ET study procedures and observations at the time of withdrawal (see Section 8.8 and Appendix A).

For patients withdrawn for reasons other than withdrawal of consent every effort should be made to complete the early termination study procedures and observations at the time of withdrawal (see Section 8.8 and Appendix A).

8.10 Concomitant Therapy and Procedures

The use of concomitant therapies or procedures defined below must be recorded on the patient's CRF. AEs related to administration of these therapies or procedures must also be documented on the appropriate CRF.

8.10.1 Concomitant Therapy

A concomitant therapy is any non-protocol specified drug or substance (including over-the-counter medications, herbal medications and vitamin supplements) administered between signing informed consent and completion of the post-treatment follow-up period. All concomitant medications/treatments and significant non-drug therapies (including supplements and assistive devices) received by a patient, including changes in the patient's current medications, must be recorded in the patient's source documents and CRF. Patients taking over the counter (OTC) omega-3 fatty acids should make every effort to remain on the same brand throughout the study.

Allowed Concomitant Therapy

Any medications deemed necessary by the Investigator are allowed except those listed in the disallowed concomitant therapy.

Disallowed Concomitant Therapy

No lipid lowering therapies (e.g., fibrates, niacin, fish oil or other products containing omega-3 fatty acids [including OTC preparations]), -glucagon-like peptide-1 (GLP-1) agonists, Glybera, or systemic corticosteroids may be started or adjusted after baseline Qualification. Doses of existing oral anti-diabetic medication, oral contraceptives, hormone replacement therapy, anticoagulants, or drugs or dietary supplements with potential lipid-altering effects should not be adjusted. Study patients are prohibited from receiving other experimental agents during the study. This includes marketed agents at experimental dosages that are being tested for the treatment of hypertriglyceridemia.

Patients should consult with the Site Investigator or designee prior to initiating any new medication, including non-prescription or herbal compounds or any other non-drug therapy.

8.10.2 Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between signing of informed consent and Week 78 visit.

Disallowed Concomitant Procedure

Plasma apheresis is not allowed during the study.

8.11 Treatment Compliance

Compliance with treatment dosing is to be monitored and recorded by Study Center staff. The Study Center staff is required to document the receipt, dispensing, and return/destruction of volanesorsen. Patients that are self-administering volanesorsen at home must record treatment in a dosing diary that will be reviewed periodically by Study Center staff and the Clinical Monitor.

9. SERIOUS AND NON-SERIOUS ADVERSE EVENT REPORTING

9.1 Sponsor Review of Safety Information

Safety information will be collected, reviewed, and evaluated by the Sponsor in accordance with the Safety Management Plan throughout the conduct of the clinical trial.

9.2 Regulatory Requirements

The Sponsor is responsible for regulatory submissions and reporting to the Investigators of serious adverse events (SAEs) including suspected unexpected serious adverse reactions (SUSARs) per the International Conference on Harmonization (ICH) guidelines E2A and ICH E6. Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines.

Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) will be notified of any SAE according to applicable regulations. The Independent DSMB will be notified of any SAE as specified in the DSMB charter.

In addition to the Investigator's assessment of relatedness, the Sponsor or designee will evaluate the available information and perform an independent assessment of relatedness. While the Sponsor may upgrade an Investigator's decision it is not permissible to downgrade the Investigator's opinion for the purposes of determining whether the SAE meets the definition of a SUSAR.

The following table identifies the SAEs that the Sponsor or designee will not report on an individual basis in an expedited manner because they are anticipated to occur in the study population independent of volanesorsen exposure. The Investigator still has the responsibility to report all SAEs to the Sponsor as described in Sections 9.4.1 to 9.4.3.5.

Table 3 Expected Event for the Protocol Defined Population by Preferred Term and the Expected Incidence

Preferred Term	Expected Incidence in the Protocol Defined Population (Gaudet et al. 2010 and 2013)
Pancreatitis associated events including the PTs of hereditary pancreatitis, pancreatitis, pancreatitis acute, pancreatitis chronic, pancreatitis necrotizing, pancreatitis relapsing	0.2-0.35 events per patient-year

Fatal pancreatitis associated events will be considered as unexpected and are reportable. The Sponsor and DSMB will monitor non-fatal pancreatitis associated SAEs using the incidence rate of the event compared to the rate expected in a non-volanesorsen exposed population. If the aggregate analysis indicates that an event is occurring significantly more frequently or at a greater severity than expected, then the event will be reported.

SAEs not specified in the table will be evaluated on case by case basis to determine whether there is a reasonable possibility that the drug caused the event. If the event is considered by the Sponsor or designee to meet the definition of a SUSAR the event will be reported.

9.3 Definitions

9.3.1 Adverse Event

An adverse event is any unfavorable and unintended sign (including a clinically-significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the study or use of investigational drug product, whether or not the AE is considered related to the investigational drug product.

9.3.2 Adverse Reaction and Suspected Adverse Reaction

An adverse reaction is any adverse event caused by volanesorsen.

A suspected adverse reaction is any adverse event for which there is a reasonable possibility that volanesorsen drug caused the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

9.3.3 Serious Adverse Event (SAE)

A serious adverse event is any adverse event that in the view of either the Investigator or Sponsor, meets any of the following criteria:

- Results in death
- Is life threatening: that is, poses an immediate risk of death at the time of the event

An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Hospitalization is defined as an admission of greater than 24 hours to a medical facility and does not always qualify as an AE
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly or birth defect in the offspring of the patient (whether the patient is male or female)
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

9.4 Monitoring and Recording Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the study (i.e., before informed consent) should be recorded as Medical History and not recorded as AEs unless the pre-existing condition worsened. The Investigator should always group signs and symptoms into a single term that constitutes a **single unifying diagnosis** if possible.

9.4.1 Serious Adverse Events

In the interest of patient safety, and in order to fulfill regulatory requirements**,** all SAEs (regardless of their relationship to volanesorsen) should be reported to the Sponsor or designee within 24 hours of the Study Center's first knowledge of the event. The collection of SAEs will begin after the patient signs the informed consent form and stop at the end of the patient's follow-up period which is defined as the Week 78 visit. When the Investigator is reporting by telephone, it is important to speak to someone in person versus leaving a message. An Initial

Serious Adverse Event Form should be completed and a copy should be faxed to the Sponsor or designee.

Detailed information should be actively sought and included on Follow-Up Serious Adverse Event Forms as soon as additional information becomes available. All SAEs will be followed until resolution. SAEs that remain ongoing past the patient's last protocol-specified follow-up visit will be evaluated by the Investigator and Sponsor. If the Investigator and Sponsor agree the patient's condition is unlikely to resolve, the Investigator and Sponsor will determine the follow-up requirement.

9.4.2 Non-Serious Adverse Events

The recording of non-serious AEs will begin after the patient signs the informed consent form and will stop at the end of the patient's follow-up period, which is defined as the Week 78 visit. The Investigator will monitor each patient closely and record all observed or volunteered AEs on the Adverse Event Case Report Form.

9.4.3 Evaluation of Adverse Events (Serious and Non-Serious)

The Investigator's opinion of the following should be documented on the Adverse Event Case Report Form:

9.4.3.1 Relationship to the Study Drug

The event's relationship to volanesorsen is characterized by 1 of the following:

- **Related:** There is clear evidence that the event is related to the use of volanesorsen, e.g., confirmation by positive rechallenge test
- **Possible:** The event cannot be explained by the patient's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and volanesorsen administration
- **Unlikely/Remote:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to volanesorsen administration and/or exposure suggests that a causal relationship is unlikely (For reporting purposes, Unlikely/Remote will be grouped together with Not Related)
- **Not Related:** The event can be readily explained by the patient's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and volanesorsen

9.4.3.2 Severity

The severity of AEs and SAEs will be graded based on criteria from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010 (refer to Appendix D). Any AE not listed in Appendix D will be graded as follows:

- **Mild:** The event is easily tolerated by the patient and does not affect the patient's usual daily activities

- **Moderate:** The event causes the patient more discomfort and interrupts the patient's usual daily activities
- **Severe:** The event is incapacitating and causes considerable interference with the patient's usual daily activities

If the event is an SAE, then all applicable seriousness criteria must be indicated (criteria listed in Section 9.3.3).

9.4.3.3 Action Taken with Volanesorsen

Action taken with volanesorsen due to the event is characterized by 1 of the following:

- **None:** No changes were made to volanesorsen administration and dose
- **Permanently Discontinued:** Volanesorsen was discontinued and not restarted
- **Temporarily Interrupted, restarted – same dose:** Dosing was temporarily interrupted or delayed due to the AE and restarted at the same dose
- **Reduced schedule:** Dosing frequency was reduced

9.4.3.4 Treatment Given for Adverse Event

Any treatment (e.g., medications or procedures) given for the AE should be recorded on the Adverse Event Case Report Form (treatment should also be recorded on the concomitant treatment or ancillary procedures CRF as appropriate).

9.4.3.5 Outcome of the Adverse Event

If the event is a non-serious AE then the event's outcome is characterized by 1 of the following:

- **AE Persists:** Patient terminates from the trial and the AE continues
- **Recovered:** Patient recovered completely from the AE
- **Became Serious:** The event became serious (the date that the event became serious should be recorded as the Resolution Date of that AE and the Onset Date of the corresponding SAE)
- **Change in Severity** (if applicable): AE severity changed

If the event is a SAE then the event's outcome is characterized by 1 of the following:

- **Ongoing:** SAE continuing
- **Persists (as non-serious AE):** Patient has not fully recovered but the event no longer meets serious criteria and should be captured as an AE on the non-serious AE eCRF (the SAE resolution date should be entered as the date of onset of that AE)
- **Recovered:** Patient recovered completely from the SAE (the date of recovery should be entered as the SAE resolution date)
- **Fatal:** Patient died (the date of death should be entered as the SAE resolution date)

9.4.4 Adjudication Committees

All SAEs that occur during the study that are consistent with a major acute cardiovascular event (MACE) will be adjudicated by a blinded, independent committee as outlined in the MACE Adjudication Charter.

All AEs and SAEs that occur during the study that are consistent with an event of acute pancreatitis will be adjudicated by a blinded, independent committee according to the Atlanta classification of acute pancreatitis (Banks et al. 2013) and as outlined in the Pancreatitis Adjudication Charter. In addition, data for prior episodes of acute pancreatitis or suspected pancreatitis will be collected by review of each patient's medical chart and these events will also be adjudicated.

9.5 Procedures for Handling Special Situations

9.5.1 Abnormalities of Laboratory Tests

Clinically-significant abnormal laboratory test results may, in the opinion of the Investigator, constitute or be associated with an AE. Examples of these include abnormal laboratory results that are associated with symptoms, or require treatment, e.g., bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac arrhythmias due to hyperkalemia. Whenever possible, the underlying diagnosis should be listed in preference to abnormal laboratory values as AEs. Clinically-significant abnormalities will be monitored by the Investigator until the parameter returns to its baseline value or until agreement is reached between the Investigator and Sponsor Medical Monitor. Laboratory abnormalities deemed not clinically-significant (NCS) by the Investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator should not be deemed NCS on the laboratory sheet.

The Investigator is responsible for reviewing and signing all laboratory reports. The signed clinical laboratory reports will serve as source documents and should include the Investigator's assessment of clinical significance of out of range/abnormal laboratory values.

9.5.2 Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the patient is hospitalized; the Study Center must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the patient's consent to participate in the study
- The condition that required the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the patient's consent to participate in the study and the timing of the procedure or treatment
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission

9.5.3 Dosing Errors

Volanesorsen dosing errors should be documented as Protocol Deviations. A brief description should be provided in the deviation, including whether the patient was symptomatic (list symptoms) or asymptomatic, and the event accidental or intentional.

Dosing details should be captured on the Dosing Case Report Form. If the patient takes a dose of volanesorsen that exceeds protocol specifications and the patient is symptomatic, then the symptom(s) should be documented as an AE and be reported per Section 9.4.

Should an overdose occur, the Investigator or designee should refer to the Guidance to Investigator's section of the Investigator's Brochure and contact the Sponsor or designee within 24 hours.

9.5.4 Contraception and Pregnancy

Male patients and female patients of childbearing potential must continue to use appropriate contraception with their partners, or refrain from sexual activity, as described in Section 6.3.1.

If a patient becomes pregnant or a pregnancy is suspected, or if a male patient makes or believes that he has made someone pregnant during the study, then the Study Center staff must be informed immediately. An Initial Pregnancy Form should be submitted to the Sponsor or designee **within 24 hours** of first learning of the occurrence of pregnancy. Follow-up information including delivery or termination is reported on Follow-up Pregnancy Forms and reported within 24 hours.

Payment for all aspects of obstetrical care, child or related care will be the patient's responsibility.

Female patients: If a suspected pregnancy occurs while on the study (including follow-up), a pregnancy test will be performed. The patient with a confirmed pregnancy will be immediately withdrawn from treatment with volanesorsen. However, the patient will be encouraged to complete the post-treatment follow-up portion of the study to the extent that study procedures do not interfere with the pregnancy. Regardless of continued study participation, the study physician will assist the patient in getting obstetrical care and the progress of the pregnancy will be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the Study Center and Sponsor may require access to the mother and infant's medical records for an additional 8 weeks after birth.

Male patients: The progress of the pregnancy in a male patient's partner should be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, **the Study Center and Sponsor may request access to the mother and infant's medical records for an additional 8 weeks after birth**. Follow-up will be performed to the extent permitted by applicable regulations and privacy considerations.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints

For fasting lipid measurements, the values at Month 3 analysis time point are defined as the average of Week 12 (Day 78) and Week 13 (Day 85) fasting assessments, the values of Month 6 analysis time point is at the end of Month 6 are defined as the average of Week 25 (Day 169) and Week 26 (Day 176) fasting assessments, and the values at the Month 12 analysis time point are defined as the average of Week 50 (Day 344) and Week 52 (Day 358) fasting assessments.

10.1.1 Efficacy Endpoints

- Percent change and absolute change from baseline in fasting TG
- Frequency and severity of patient reported abdominal pain during the treatment period
- Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-HDL-C, apoB, HDL-C, apolipoprotein A-1 (apoA-1), VLDL-C, and LDL-C
- Percent change from baseline in fasting total apolipoprotein C-III
- Quality of Life questionnaires (EQ-5D, SF-36)
- Adjudicated acute pancreatitis event rate
- Other symptoms: eruptive xanthoma, lipemia retinalis

10.1.2 Safety Endpoints

- Adverse events including adjudicated events of pancreatitis and MACE
- Vital signs and weight
- Physical examinations
- Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis)
- Echocardiography
- Electrocardiograms (ECGs)
- Use of concomitant medications
- MRIs

10.2 Sample Size

No sample size calculations were performed as this is an open-label study.

10.3 Populations

Full Analysis Set (FAS): All patients who are enrolled and received at least 1 dose of active Study Drug and have a baseline TG assessment. The FAS represents the practically-feasible intent-to-treat (ITT) population as delineated in ICH Guideline E9.

Per Protocol Set (PPS): Subset of the FAS who received 9 of first 13 scheduled doses of volanesorsen and with no significant protocol deviations that would be expected to affect efficacy and PD assessments. The detailed criteria will be specified and finalized prior to the final database lock.

Safety Set: All patients who are enrolled and receive at least 1 dose of volanesorsen.

PK Population: All patients who are enrolled, receive at least 1 dose of volanesorsen, and have at least 1 post first dose PK sample collected, analyzed, and reported.

10.4 Definition of Baseline

Definitions of baseline are given below for the purposes of the final analysis.

For fasting lipid measurements, 2 baselines are defined for each patient in Groups 1 and 2: Group 1 (ISIS 304801-CS6) or Group 2 (ISIS 304801-CS16) index study baseline and the baseline in this open-label study, which is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 (e.g., qualification assessments or assessments from final visit of the ISIS 304801-CS6 or ISIS 304801-CS16 index studies if used for qualification).

For other measurements, baseline for patients on active treatment in the ISIS 304801-CS6 or ISIS 304801-CS16 index study will be the ISIS 304801-CS6 or ISIS 304801-CS16 index study baseline. For patients on placebo in the ISIS 304801-CS6 or ISIS 304801-CS16 index study, baseline will be the last non-missing assessment prior to the first dose of Study Drug. Details will be provided in the SAP.

10.5 Interim Analysis

An interim analysis may be conducted after the last patient's Week 13 visit of the open-label study or after the database of the ISIS 304801-CS6 and ISIS 304801-CS16 index studies are locked and unblinded. Both safety and efficacy information from this open-label study may be summarized during this interim analysis. Efficacy analyses will be detailed in the SAP.

10.6 Planned Methods of Analysis

All eCRF data, lab data transfers, as well as any outcomes derived from the data, will be provided in the patient data listings. Patient data listings will be presented for all patients enrolled into the study. Descriptive summary statistics including n, mean, median, standard deviation, standard error, interquartile range (25th percentile, 75th percentile), and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data by treatment group of the index studies for patients on active Study Drug in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies, and pooled treatment naïve group which includes patients on placebo in index studies. Where appropriate, p-values will be reported. All statistical tests will be conducted using 2-sided tests with 5% Type I error rates unless otherwise stated.

TG related endpoints will be assessed in the FAS and PPS, and all other efficacy endpoints will be assessed in the FAS. All safety assessments will be performed on the Safety Set. PK endpoints will be assessed in the PK Set as applicable.

10.6.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics by treatment group and overall. The patient disposition will be summarized by treatment group and overall. All patients enrolled will be included in a summary of patient disposition.

10.6.2 Safety Analysis

Treatment duration and amount of Study Drug received will be summarized by treatment group and overall.

Patient incidence rates of AEs will be tabulated by MedDRA system organ class, MedDRA preferred term, and treatment group of the index studies. Narratives of treatment-emergent deaths, serious and significant AEs, including early withdrawals due to AEs, will also be provided.

All treatment-emergent AEs, all treatment-emergent AEs potentially related to Study Drug, all treatment-emergent serious AEs, and all treatment-emergent serious AEs potentially related to Study Drug will be summarized.

Injection Site Reactions (ISRs) will be summarized by treatment group, MedDRA preferred term and severity.

Independently adjudicated events of MACE and pancreatitis will be summarized by treatment group.

Laboratory tests to ensure patient safety including chemistry panel, complete blood count (CBC) with differential, coagulation panel, IM, complement etc., will be summarized by study visits by treatment group.

These safety variables will also be presented as change and percent change from baseline over time after Study Drug administration, as appropriate.

Vital signs, weight, ECG measures, echocardiography assessments, and MRI assessments will be tabulated by treatment group.

10.6.3 Efficacy Analysis

Percent change and change from baseline to Month 3, Month 6, and Month 12 in fasting TG will be summarized by treatment group. Response rate of patients with fasting plasma TG < 750 mg/dL or achieving fasting TG $\geq 40\%$ reduction from baseline at Month 3, Month 6, and Month 12 will be summarized. Response analysis will also be conducted using a range of fasting plasma TG thresholds for determination of responder status.

Percent change and change from baseline to Month 3, Month 6, and Month 12 will also be summarized by treatment group for other fasting lipid measures including non-HDL-C, apoB, HDL-C, apoA-1, VLDL-C, and LDL-C, total cholesterol, and fasting total apoC-III.

The incremental effects of volanesorsen on lipid measures will be explored and the association between changes in lipid parameters and total amount of drug received will be examined, as appropriate.

Frequency and severity of patient reported abdominal pain, adjudicated acute pancreatitis event rate, quality of life assessments, and comparison of other symptoms including eruptive xanthomas and lipemia retinalis will be summarized by treatment group.

Additional details of the analyses to be conducted will be provided in the SAP.

10.6.4 Pharmacokinetic and Immunogenicity Analysis

10.6.4.1 Pharmacokinetic Analysis

For all patients, pre-dose and post-treatment volanesorsen plasma concentrations will be summarized using descriptive statistics by treatment group and IM status.

For patients in the PK subgroup only, non-compartmental PK analysis of volanesorsen will be carried out on each individual patient data set using data collected in the open-label study from the intensive PK subgroup, following a single-dose (i.e., single-dose PK) or multiple doses (i.e., steady-state PK), depending on their earlier treatment in the index studies (Group 1 and 2 patients). On Week 1 Day 1 of the open-label study, patients who received placebo in the index study will receive the first treatment of volanesorsen (single-dose PK), while patients who received volanesorsen in the index studies had been on volanesorsen treatment for 12 months (ISIS 304801-CS6) or 6 months (ISIS 304801-CS16), thus the PK data collected from these patients reflect steady-state PK. The maximum observed drug concentration (C_{max}) and the time taken to reach C_{max} (T_{max}) will be obtained directly from the concentration-time data. Area under the plasma concentration-time curve from time zero to 24 hours (AUC_{0-24h}) will be calculated using the linear trapezoidal rule. Apparent systemic (plasma) clearance after SC administration (CL_{0-24h} /F) will be calculated from CL_{0-24h} /F = Actual Dose/AUC_{0-24h}. Mean residence time (MRT) from time zero to 24 hours after the SC administration will be calculated from the equation, $MRT_{0-24h} = AUMC_{0-24h}/AUC_{0-24h}$, where $AUMC_{0-24h}$ is the area under the moment plasma concentration-time curve from time zero to 24 hours after the SC administration. Other PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist.

Plasma PK parameters will be summarized using descriptive statistics by treatment group and IM status. Additional details regarding the PK analysis will be described in the SAP.

Population PK, PK/PD, and covariate analysis may be performed if deemed appropriate, and results will be reported separately.

10.6.4.2 Immunogenicity Analysis

Immunogenicity (IM) results (screen positive/negative, confirmed positive/negative or not evaluable, and when applicable, titer of anti-volanesorsen antibodies) before, during, and after treatment with Study Drug (volanesorsen) (i.e., sample [anti-drug antibody] ADA status) will be listed by their prior treatment in study ISIS 304801-CS6 or ISIS 304801-CS16 (Groups 1 and 2) and study day. Subject ADA status (positive/negative or not evaluable) for all evaluable patients, along with the study day associated with the first positive IM status emerged (T_{first}, i.e., onset of ADA development), the last positive IM status observed (T_{last}), the last ADA sample collection day, and subject - peak titer if applicable, will be listed by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16 (Groups 1 and 2) and study day. Subjects with

positive anti-volanesorsen antibody status may be further classified (when applicable) as being either 'persistent', 'transient', or 'not determinable', if deemed appropriate.

Additionally, the sample and subject IM incidence (number) and incidence rate (percent) will be summarized as the total number and percent of evaluated subjects with antibody negative, positive, and unknown status by treatment group. Furthermore, onset and titer of the ADA response, if applicable, will be summarized as median, quartiles (25% and 75%), and range.

Additional details regarding the IM data analysis will be described in the SAP.

Potential relationships between immunogenicity results (e.g., IM status) and selected efficacy (e.g., %change in fasting TG from baseline at 3-, 6-, and 12-month endpoints), safety, and PK (e.g., C_{trough}) measures will be evaluated using graphical analysis and statistical analysis. These analyses will be either conducted and included in the study report, or data pooled and analyzed from all available Phase 2 and 3 studies and reported separately.

11. INVESTIGATOR'S REGULATORY OBLIGATIONS

11.1 Informed Consent

The written informed consent document should be prepared in the language(s) of the potential patient population, based on an English version provided by the Sponsor.

Before a patient's participation in the trial, the Investigator is responsible for obtaining written informed consent from the patient after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific qualification procedures or any Study Drug are administered. The patient must be given sufficient time to consider whether to participate in the study.

The acquisition of informed consent and the patient's agreement or refusal to notify his/her primary care physician should be documented in the patient's medical records and the informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion (not necessarily an Investigator). The original signed informed consent form should be retained in the Study Master File and in any other locations required by institutional policy, and a copy of the signed consent form should be provided to the patient.

11.2 Ethical Conduct of the Study

The Guidelines of the World Medical Association (WMA) Declaration of Helsinki dated October 2002 the applicable regulations and guidelines of current Good Clinical Practice (GCP) as well as the demands of national drug and data protection laws and other applicable regulatory requirements will be strictly followed.

11.3 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent form, other written patient information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by the Sponsor before recruitment of patients into the study and shipment of volanesorsen. A copy of

the written approval of any other items/materials that must be approved by the Study Center or IEC/IRB must also be received by the Sponsor before recruitment of patients into the study and shipment of Study Drug. The Investigator's Brochure must be submitted to the IEC/IRB for acknowledgement.

The Investigator must submit to and, where necessary, obtain approval from the IEC/IRB, for all subsequent protocol amendments and changes to the informed consent document. The Investigator should notify the IEC/IRB of deviations from the protocol in accordance with ICH GCP Section 4.5.2. The Investigator should also notify the IEC/IRB of serious adverse events occurring at the Study Center and other adverse event reports received from the Sponsor, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study. Copies of the Investigator's reports, all IEC/IRB submissions and the IEC/IRB continuance of approval must be sent to the Sponsor.

11.4 Patient Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained. On the case report forms (CRF) or other documents submitted to the Sponsor, patients should be identified by unique initials and a patient study number only. Documents that are not for submission to the Sponsor (e.g., signed informed consent forms) should be kept in strict confidence by the Investigator.

In compliance with Federal and local regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the patient to permit named representatives to have access to his/her study-related records without violating the confidentiality of the patient.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments

Protocol amendments must be made only with the prior approval of the Sponsor. Agreement from the Investigator must be obtained for all protocol amendments and amendments to the informed consent document. The regulatory authority and IEC/IRB must be informed of all amendments and give approval for any amendments likely to affect the safety of the patients or the conduct of the trial. The Investigator **must** send a copy of the approval letter from the IEC/IRB to the Sponsor.

12.2 Study Termination

The Sponsor reserves the right to terminate the study according to the terms of the site contract. The Investigator reserves the right to terminate their participation in the study, according to the terms of the site contract. The Investigator/Sponsor should notify the IEC/IRB in writing of the trial's completion or early termination and send a copy of the notification to the Sponsor.

12.3 Study Documentation and Storage

An electronic case report form (eCRF) utilizing an Electronic Data Capture (EDC) application will be used for this study.

The Investigator should ensure that all appropriately qualified persons to whom he/she has delegated trial duties are recorded on a Sponsor-approved Delegation of Site Responsibilities Form.

Source documents are original documents, data, and records from which the patient's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, imaging, and correspondence. In this study, CRFs may not be used as source documents.

The Investigator and Study Center staffs are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation in accordance with Section 8 of the ICH Guidelines (E6), suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Elements should include:

- Patient files containing completed CRFs, informed consents, and supporting copies of source documentation
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation and all correspondence to and from the IEC/IRB and the Sponsor
- If volanesorsen supplies are maintained at the Study Center, proof of receipt, volanesorsen Accountability Record, Return of volanesorsen for Destruction, final study volanesorsen reconciliation, and all volanesorsen-related correspondence

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

No study document should be destroyed without prior written agreement between the Sponsor or and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor.

12.4 Study Monitoring

The Sponsor representative and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the trial (e.g., CRFs and other pertinent data) provided that patient confidentiality is respected.

The Sponsor monitor is responsible for inspecting the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to patient medical records and other study-related records needed to verify the entries on the CRFs.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's Clinical Quality Assurance Department. Inspection of Study Center facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the trial conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

To ensure the quality of clinical data a clinical data management review will be performed on patient data received by the Sponsor. During this review, patient data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or Study Center notifications will be sent to the Study Center for completion and return to Sponsor.

The Principal Investigator will sign and date the indicated places on the CRF. These signatures will indicate that the principal Investigator inspected or reviewed the data on the CRF, the data queries, and the Study Center notifications, and agrees with the content.

12.5 Language

Case report forms must be completed in English. Generic names for concomitant medications should be recorded in English if possible, unless it is a combination drug, then record the trade name in English.

All written information and other material to be used by patients and investigative staff must use vocabulary and language that are clearly understood.

12.6 Compensation for Injury

The Sponsor maintains appropriate insurance coverage for clinical trials and will follow applicable local compensation laws. Patients will be treated and/or compensated for any study-related illness/injury in accordance with the information provided in the Compensation for Injury section of the Informed Consent document.

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14. APPENDICES

Appendix A Schedule of Procedures

Qualification through Treatment Period

Post-Treatment Follow-up

Appendix A Schedule of Procedures – Qualification through Treatment Period

Study Period		Qual[a]	Treatment Period																							
Study Week		-2 to -1	Wk 1		Wk 2.5	Wk 4	Wk 6	Wk 8	Wk 10	Month 3		Wk 15 & 17	Wk 19	Wk 21 & 23	Month 6		Wk 28 & 30	Wk 32	Wk 34 & 36	Wk 38	Wk 40 & 42	Wk 44	Wk 46 & 48	Month 12	
										Wk 12	Wk 13				Wk 25	Wk 26								Wk 50	Wk 52 or ET
Study Day		-14 to -7	1	2	11	22	36	50	64	78	85	99 & 113	127	141 & 155	169	176	190 & 204	218	232 & 246	260	274 & 288	302	316 & 330	344	358
Visit Window+/- Days		0	0	0	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Informed Consent		X																							
Outpatient Visit		X	X	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X	X[j]	X[j]	X[j]	X[j]	X	X[j]	X[j]	X[j]	X	X[j]	X[j]	X[j]	X[j]	X
Inclusion/Exclusion Criteria		X																							
Vital Signs + body weight (+ height on Day 1 only)		X	X			X		X			X					X				X					X
Physical Examination		X	X								X					X				X					X
12- lead ECG (triplicate)		X									X					X				X					X
MRI (liver/spleen)		X																							X[k]
Echocardiography		X														X[k]									X[k]
Blood Draw (Fasting)[c]	Chemistry Panel	X	X			X		X			X		X			X		X		X		X			X
	CBC with Differential[b]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Serum Lipid Panel	X	X			X		X		X	X				X	X				X				X	X
	Coagulation (aPTT, PT, INR)	X						X			X					X				X					X
	hsCRP, HbA1c, FPG, and de-lipidated free glycerol	X[n]	X								X					X									X
	Sedimentation Rate		X								X					X									X
	Complement (C5a, Bb)		X								X					X									X
	Plasma PK - Volanesorsen		X[l]	X		X		X			X					X				X					X
	Anti-Volanesorsen Antibodies		X			X		X			X					X				X					X
	FSH (women only, if applicable)	X																							
	Serum Pregnancy Test[d]	X				X		X			X		X			X		X		X		X			X
	Archived Serum & Plasma Samples[e]		X					X			X					X									X
	Troponin I[o]	X																							

Appendix A Schedule of Procedures - Qualification through Treatment Period *Continued*

Study Period	Qual[a]	Treatment Period																						
Study Week	-2 to -1	Wk 1		Wk 2.5	Wk 4	Wk 6	Wk 8	Wk 10	Month 3		Wk 15 & 17	Wk 19	Wk 21 & 23	Month 6		Wk 28 & 30	Wk 32	Wk 34 & 36	Wk 38	Wk 40 & 42	Wk 44	Wk 46 & 48	Month 12	
									Wk 12	Wk 13				Wk 25	Wk 26								Wk 50	Wk 52 or ET
Study Day	-14 to -7	1	2	11	22	36	50	64	78	85	99 & 113	127	141 & 155	169	176	190 & 204	218	232 & 246	260	274 & 288	302	316 & 330	344	358
Visit Window+/- Days	0	0	0	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Urinalysis[c]	X	X[m]			X		X			X[m]		X[m]			X[m]		X[m]		X[m]		X[m]			X[m]
Fundus Photography[f]	X																							X[k]
Genetic testing for FCS diagnosis (if not available in medical history)[g]	X																							
Weekly Study Drug: SC Injection		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Symptom Diary (weekly)	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Assessment(s)		X								X					X									X
Food/Drink Diary (quarterly)[h]		X								X					X									X
Diet/Alcohol Counseling[i]	X	X			X		X			X					X				X					X
Adverse Events	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Appendix A Schedule of Procedures – Post-Treatment Follow-up

Study Period		Post Treatment Follow-up[p]				
Study Week		Wk 54 & 56	Wk 58	Wk 65	Wk 71	Wk 78
Study Day		372 & 386	400	449	491	540
Visit Window+/- Days		2	7	7	7	7
Informed Consent						
Outpatient Visit		X[l]	X[l]	X	X[l]	X
Inclusion/Exclusion Criteria						
Vital Signs + body weight (+ height on Day 1 only)				X		X
Physical Examination				X		X
12- lead ECG (triplicate)				X		X
MRI (liver/spleen)						
Echocardiography						
Blood Draw (Fasting)[c]	Chemistry Panel		X	X	X	X
	CBC with Differential[b]	X	X	X	X	X
	Serum Lipid Panel			X		X
	Coagulation (aPTT, PT, INR)					
	hsCRP, HbA1c, FPG, and de-lipidated free glycerol			X		X
	Sedimentation Rate			X		X
	Complement (C5a, Bb)			X		X
	Plasma PK - Volanesorsen			X		X
	Anti-Volanesorsen Antibodies			X		X
	FSH (women only, if applicable)					
	Serum Pregnancy Test[d]		X	X	X	X
	Archived Serum & Plasma Samples[e]			X		X
	Troponin I[o]					

Appendix A Schedule of Procedures – Post-Treatment Follow-up *Continued*

Study Period	Post Treatment Follow-up[p]				
Study Week	**Wk 54 & 56**	**Wk 58**	**Wk 65**	**Wk 71**	**Wk 78**
Study Day	**372 & 386**	**400**	**449**	**491**	**540**
Visit Window+/- Days	**2**	**7**	**7**	**7**	**7**
Urinalysis[c]		X[m]	X[m]	X[m]	X[m]
Fundus Photography[f]					
Genetic testing for FCS diagnosis (if not available in medical history)[g]					
Weekly Study Drug: SC Injection					
Symptom Diary (weekly)	X	X	X	X	X
Quality of Life Assessment(s)			X		X
Food/Drink Diary (quarterly)[h]			X		X
Diet/Alcohol Counseling[i]		X	X	X	X
Adverse Events	X	X	X	X	X
Concomitant Medication	X	X	X	X	X

Appendix A Schedule of Procedures *Continued*

a Qualification procedures performed (Please refer to Sections 3.4, 4.1, and 6.1.2)

b Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1 week and determined not to have met a stopping rule before dosing can continue. If there is no reportable platelet count within 14 days of the last platelet count, the Investigator will contact the patient to hold dosing until a new platelet count is obtained and reviewed. All platelet count results will be promptly reviewed by the Investigator to ensure that the count has not met the stopping rule and to determine whether the rate of decline is suggestive that the patient could be approaching the dose pause rule of 75,000/mm^3. In the event of any platelet count less than 50,000/mm^3 or a rate of decline ≥ 50% between two consecutive assessments, irrespective of the platelet level, then dosing of a patient with Study Drug (ISIS 304801 or placebo) will be stopped permanently. Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor

c Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours. During treatment period urine and blood samples will be collected prior to Study Drug administration. Does not apply to 24-hour PK blood draw

d Females of childbearing potential only

e Serum and plasma samples will be collected and stored for follow-up exploration of laboratory findings and/or adverse events (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.) in this or subsequent clinical studies of volanesorsen

f If possible, fundus photography should be completed prior to administration of the first dose of Study Drug (Group 2 ISIS 304801-CS16 roll over patients) and repeated at Week 52 (Please refer to Section 6.2.2.2)

g Genetic testing can be conducted for study Qualification (Group 2 ISIS 304801-CS16 roll over patients); genetic testing will only be conducted if allowed in the geographic region and only after the patient has given specific written informed consent for genetic testing

h In addition to diary, patients will be contacted at random times during the study to review their current eating and drinking habits

i To reinforce compliance to the diet and alcohol restrictions. Random diet/alcohol assessments (phone visits) will also be performed by dietician or study personnel

j Assessments and procedures to be conducted by either a home healthcare nurse, or the Study Center as arranged by the Study Center personnel

k A ± 7-day window is allowed for MRI, echocardiography procedures and fundus photography

l Full or abbreviated PK profile (see Appendix C)

m Expanded urinalysis (see Appendix B)

n HbA1c only

o All abnormal troponin samples will be rerun at the central laboratory and also analyzed for CK-MB

p If needed, the post-treatment follow-up period will be extended (with patients monitored every 6 weeks) until apoC-III levels return to baseline values

Appendix B List of Laboratory Analytes

Appendix B List of Laboratory Analytes

Based on emerging data from this or future studies, additional tests not listed below may be performed on stored samples to better characterize the profile of volanesorsen or other similar oligonucleotides.

Clinical Chemistry Panel

- Sodium
- Potassium
- Chloride
- Bicarbonate
- Total protein
- Albumin
- Calcium
- Magnesium
- Phosphorus
- Glucose
- BUN
- Creatinine
- Uric Acid
- Total bilirubin
- Direct (conjugated) bilirubin
- Indirect (unconjugated) bilirubin
- ALT
- AST
- Alkaline phosphatase

Coagulation

- aPTT (sec)
- PT (sec)
- INR

Lipid Panel

- Total Cholesterol
- LDL-C
- HDL-C
- Triglycerides
- Non-HDL-C
- VLDL-C
- apoA-1
- apoB
- apoC-III

Hematology

- Red blood cells
- Hemoglobin
- Hematocrit
- MCV, MCH, MCHC
- Platelets
- White blood cells
- WBC Differential (% and absolute)
  - Neutrophils
  - Eosinophils
  - Basophils
  - Lymphocytes
  - Monocytes

Pharmacokinetics[1] & Immunogenicity

- Volanesorsen levels in plasma
- Anti-volanesorsen antibodies in plasma

Other Assessments

- hsCRP
- Sedimentation Rate
- C5a, Bb
- De-lipidated free glycerol
- HbA1c, FPG

Urinalysis

- Color
- Appearance
- Specific gravity
- pH
- Protein
- Blood
- Ketones
- Urobilinogen
- Glucose
- Bilirubin
- Leukocyte esterase
- Nitrate
- Microscopic examination[2]

Additional Measures for Expanded Urinalysis

- Total protein (quantitative)
- Microalbumin
- β2-microglobulin

1 Plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, IM testing (or possibly for purposes of IM assay development and/or validation), or to assess other actions of volanesorsen with plasma constituents

2 Will be performed on abnormal findings unless otherwise specified

Appendix C Pharmacokinetic Sampling Schedule

Appendix C Pharmacokinetic Sampling Schedule

Blood samples for the determination of plasma volanesorsen concentrations will be collected prior to dosing, and at various times throughout the dosing and post-treatment follow-up period as noted in the tables below.

PK Sampling Schedule (All Patients except PK Subgroup)

Week	Wk 1	Wk 4	Wk 8	Wk 13	Wk 26	Wk 38	Wk 52	Wk 65	Wk 78
Study Day	D1	D22	D50	D85	D176	D260	D358	D449	D540
Visit Window +/- Days	0	2	2	2	2	3	2	7	7
Time Point	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime	Anytime

PK Sampling Schedule (PK Subgroup only*)

Week	Wk 1	Wk 1	Wk 4	Wk 8	Wk 13	Wk 26	Wk 38	Wk 52	Wk 65	Wk 78
Study Day	D1	D2	D22	D50	D85	D176	D260	D358	D449	D540
Visit Window +/- Days	0	0	2	2	2	2	3	2	7	7
Time Point	Pre-dose, 1, 2, 3, 4, 6, 8, and 12 hrs post-dose	24 hrs Post-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime	Anytime

* Patients at selected sites will be asked to participate in the extended 24-hour PK profile beginning on Study Day 1. Participation is optional

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

The following grading recommendations for adverse events relating to lab test abnormalities are based upon the **Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010**

Adverse Event	Mild	Moderate	Severe
Hematology			
aPTT prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage
Eosinophils increased†	650 – 1,500 cell/mm^3	1,501 - 5,000 cell/mm^3	>5,000 cell/mm^3
Fibrinogen decreased	<1.0 - 0.75 x LLN or <25% decrease from baseline	<0.75 - 0.5 x LLN or 25 - <50% decrease from baseline	<0.5 x LLN or ≥50% decrease from baseline
Hemoglobin decreased (Anemia)	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated
Hemoglobin increased	Increase in >0 - 2 g/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 g/dL above ULN or above baseline if baseline is above ULN	Increase in >4 g/dL above ULN or above baseline if baseline is above ULN
INR increased	>1 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation
Lymphocyte count decreased	<LLN - 800/mm^3; <LLN - 0.8 x 10^9/L	<800 - 500/mm^3; <0.8 - 0.5 x 10^9 /L	<500 /mm^3; <0.5 x 10^9 /L
Lymphocyte count increased	-	>4000/mm^3 - 20,000/mm^3	>20,000/mm^3
Neutrophil count decreased	<LLN - 1500/mm^3; <LLN - 1.5 x 10^9 /L	<1500 - 1000/mm^3; <1.5 - 1.0 x 10^9 /L	<1000/mm^3; <1.0 x 10^9 /L
Platelet count decreased	<LLN - 75,000/mm^3; <LLN - 75.0 x 10^9 /L	<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9 /L	<50,000/mm^3; <50.0 x 10^9 /L
White blood cell decreased	<LLN - 3000/mm^3; <LLN - 3.0 x 10^9 /L	<3000 - 2000/mm^3; <3.0 - 2.0 x 10^9 /L	<2000/mm^3; <2.0 x 10^9 /L
Chemistry			
Acidosis	pH <normal, but >=7.3	-	pH <7.3
Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Alkalosis	pH >normal, but ≤7.5	-	pH >7.5
Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 x ULN
Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

Adverse Event	Mild	Moderate	Severe
Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer
CD4 lymphocytes decreased	<LLN - 500/mm^3; <LLN - 0.5 x 10^9 /L	<500 - 200/mm^3; <0.5 - 0.2 x 10^9 /L	<200/mm^3; <0.2 x 10^9 /L
CPK increased*	>ULN - <6 ULN	6 - 10 x ULN	>10 x ULN
Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 x ULN
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 mg/dL; >3.1 mmol/L; Ionized calcium >1.6 mmol/L; hospitalization indicated
Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 mg/dL; >13.9 mmol/L; hospitalization indicated
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0; hospitalization indicated
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 mg/dL; >1.23 mmol/L
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 mmol/L; hospitalization indicated
Hyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 mg/dL; <1.75 mmol/L; Ionized calcium <0.9 mmol/L; hospitalization indicated
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 mg/dL; <3.0 mmol/L	<40 mg/dL (<2.2 mmol/L) AND requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions‡
Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 mmol/L; hospitalization indicated
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 mg/dL; <0.4 mmol/L
Hyponatremia	<LLN - 130 mmol/L	-	<130 mmol/L
Hypophosphatemia	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 mg/dL; <0.6 mmol/L
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

Adverse Event	Mild	Moderate	Severe
Urine			
Proteinuria Adults Children	1+ proteinuria; urinary protein <1.0 g/24 hrs -	2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs; Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Urinary protein ≥3.5 g/24 hrs; Urine P/C >1.9
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated

†Grading for this parameter is derived from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007

*Grading for this parameter is derived from the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0, Nov 2014

‡Modified for consistency with the ADA and Endocrine Society Guidelines (Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. Diabetes Care 2013;36:1384-95)

Sponsor:
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ISIS 304801-CS7

The APPROACH Open-Label Study

Volanesorsen (ISIS 304801)

An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol Amendment 6 - Netherlands – 11 April 2017

EudraCT No: 2015-003755-21

ISIS 304801-CS7

The APPROACH Open-Label Study

Volanesorsen (ISIS 304801)

An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol Amendment 6 - Netherlands – 11 April 2017

Protocol History:

Original Protocol:	28 August 2015
Protocol Amendment 1:	2 February 2016
Protocol Amendment 2:	22 April 2016
Protocol Amendment 3:	9 May 2016
Protocol Amendment 4:	6 June 2016
Protocol Amendment 5:	6 July 2016

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Ionis Protocol Number: ISIS 304801-CS7

Protocol Amendment 6 - Netherlands

EudraCT No: 2015-003755-21

Clinical Phase: 3

The APPROACH Open-Label Study

Volanesorsen (ISIS 304801)

An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

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Date: 11 April 2017

Confidentiality Statement

This document contains confidential information of Ionis Pharmaceuticals, Inc., that must not be disclosed to anyone other than the recipient study staff and members of the independent ethics committee, institutional review board, or authorized regulatory agencies. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc.

Protocol Signature Page

Protocol Number:	ISIS 304801-CS7
Protocol Title:	An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Amendment:	Amendment 6 Netherlands
Date:	11 April 2017

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)", dated 11 April 2017, and agree to conduct the study as described herein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice (E6).

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc.

Investigator's Signature

Investigator's Name *(please print)*

Date (DD Month YYYY)

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PROTOCOL AMENDMENT

Protocol Number: ISIS 304801-CS7

Protocol Title: An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Amendment Number: 6 - Netherlands

Amendment Date: 11 April 2017

The purpose of this protocol amendment is to implement the following modifications to Protocol ISIS 304801-CS7 Amendment 5 dated 6 July 2016:

1. To update the platelet safety monitoring rules shown in Table 3.
2. To exclude enrollment of FCS patients in this open-label study who did not participate in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies.
3. To add post heparin plasma LPL activity of ≤ 20% of normal in medical history as an inclusion criteria for ISIS 304801-CS16 (Group 2) patients as has been allowed for ISIS 304801-CS6 (Group 1) patients.
4. To allow patients who complete the 52-week treatment period to participate in an expanded access program or continue dosing for up to an additional 52 weeks until an expanded access program is approved and available in their country. Patients not participating in an expanded access program will enter the 13-week post-treatment evaluation period.
5. Added archive blood sample for potential gene sequencing related to hypertriglyceridemia (Group 2 if not available from index study).
6. Added: Troponin I, platelet bound autoantibody testing at baseline (may be done), and Table 2 Labs to be performed in the event of a platelet count Less than the Lower Limit of Normal (x2) or < 100,000/mm^3 (x1) to provided added patient safety; blood viscosity (may be done) to assess potential benefit of ISIS 304801 administration; and platelet aggregation (may be done) to assess platelet function.

Minor changes (not included in the list of changes below) have been made throughout the protocol to correct errors and/or to improve the overall clarity of the original protocol but these changes do not impact subject safety, exposure, or the overall study design.

The following table provides a summary list of major changes to the protocol, additions are indicated as underline and deletions are indicated as strikethrough:

Protocol Section	Description of Change	Rationale
Synopsis Section 3.1 Study Design	This is a multi-center open-label study of: Group 1: ISIS 304801-CS6 (index study) roll-over FCS patients Group 2: ISIS 304801-CS16 (index study) roll-over FCS patients ~~Group 3: FCS patients who did not participate in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies~~ All patients will receive volanesorsen 300 mg once per week for 52 weeks. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period. Following the Week 52 visit, patients will have the option of participating in an expanded access program or continuing dosing for up to an additional 52 weeks until an expanded access program is approved and available in their country. Patients not participating in an expanded access program will enter a 13-week post-treatment evaluation period	To exclude enrollment of FCS patients in this open-label study who did not participate in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies.
Synopsis Section 5.1 Inclusion Criteria	3. Groups 1 and 2: Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement. Group~~s 2 and 3~~: Patients who enrolled in ISIS 304801-CS16 must also meet the following criteria in order to enter into the open-label study: c. Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at ~~Screening~~Qualification for the ISIS 304801-CS16 index study ~~Group 3: Fasting TG ≥ 750 mg/dL at Screeningfor this open-label study~~	To exclude enrollment of FCS patients in this open-label study who did not participate in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies.
Synopsis Section 5.1 Inclusion Criteria	b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) supported by documentation of at least 1 of the following: • Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1) • Post heparin plasma LPL activity of ≤ 20% of normal in medical history. Note: testing of LPL activity should not be performed to confirm eligibility for the study	To add LPL activity of ≤ 20% of normal in medical history as an inclusion criteria for Group 2 patients as has been allowed for Group 1 patients.
Synopsis Section 5.2 Exclusion Criteria	~~**Exclusion Criteria for Group 3 (patients who did not participate in an index study)**~~ ~~1. Diabetes mellitus with any of the following:~~ ~~a. Newly diagnosed within 12 weeks of screening~~ ~~b. HbA1c ≥ 9.0% at Screening~~ ~~c. Recent change in anti-diabetic pharmacotherapy (change in dosage or addition of new medication within 12 weeks of screening [with the exception of ± 10 units of insulin])~~ ~~d. Anticipated need to change dose or type of medication during the treatment period of the Study (with the exception of ± 10 units of insulin)~~ ~~e. Current use of GLP-1 agonists~~ ~~2. Severe hypertriglyceridemia other than due to familial chylomicronemia syndrome~~ ~~3. Active pancreatitis within 4 weeks prior to screening~~	To exclude enrollment of FCS patients in this open-label study who did not participate in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies.

Protocol Section	Description of Change	Rationale
Synopsis Section 5.2 Exclusion Criteria *Continued*	~~4. History within 6 months of screening of acute or unstable cardiac ischemia (myocardial infarction, acute coronary syndrome, new onset angina), stroke, transient ischemic attack or unstable congestive cardiac failure requiring a change in medication or major surgery within 3 months of screening~~ ~~5. Any of the following laboratory values at Screening~~ ~~a. Hepatic:~~ ~~• Total bilirubin > upper limit of normal (ULN), unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL~~ ~~• ALT > 2.0 x ULN~~ ~~• AST > 2.0 x ULN~~ ~~b. Renal:~~ ~~• Persistently positive (2 out of 3 consecutive tests ≥ 1+) for protein on urine dipstick. In the event of a positive test eligibility may be confirmed by a quantitative total urine protein measurement of < 500 mg/24 hrs~~ ~~• Persistently positive (2 out of 3 consecutive tests ≥ trace positive) for blood on urine dipstick. In the event of a positive test eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field~~ ~~• Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault < 50 mL/min (MDRD or CKD-EPI formulas can be used instead of Cockcroft-Gault for estimation of GFR in patients with low body weight after discussion with Sponsor Medical Monitor)~~ ~~c. Cardiac Troponin I > ULN at Screening~~ ~~d. LDL-C > 130 mg/dL at Screening~~ ~~e. Any other laboratory abnormalities which, in the opinion of the Investigator or the Sponsor, would make the patient unsuitable for inclusion~~ ~~6. Uncontrolled hypertension (BP > 160/100 mm Hg)~~ ~~7. History of bleeding diathesis or coagulopathy or clinically-significant abnormality in coagulation parameters at Screening~~ ~~8. History of heart failure with NYHA greater than Class II~~ ~~9. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1~~ ~~10. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B~~ ~~11. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated~~ ~~12. Treatment with another investigational drug, biological agent, or device within 1 month of screening, or 5 half-lives of investigational agent, whichever is longer~~ ~~13. Unwilling to comply with lifestyle requirements (Section 6.3)~~	To exclude enrollment of FCS patients in this open-label study who did not participate in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies.

Protocol Section	Description of Change	Rationale
Synopsis Section 5.2 Exclusion Criteria *Continued*	~~14. Use of any of the following:~~ ~~a. Statins, omega-3 fatty acids (prescription and OTC), or fibrates unless on a stable dose for at least 3 months prior to screening and dose and regimen expected to remain constant during the treatment period. Patients taking OTC omega-3 fatty acids should make every effort to remain on the same brand throughout the study~~ ~~b. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to screening~~ ~~c. Systemic corticosteroids or anabolic steroids within 6 weeks prior to screening unless approved by the Sponsor Medical Monitor~~ ~~d. Atypical antipsychotic medications (e.g., olanzapine and clozapine) unless on a stable dose for at least 3 months prior to screening and dose and regimen expected to remain stable throughout the study~~ ~~e. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to screening and dose and regimen expected to remain constant during the treatment period~~ ~~f. Glybera gene therapy within 2 years prior to screening~~ ~~g. Oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, and apixaban) unless on a stable dose for at least 4 weeks prior to screening and regular clinical monitoring is performed~~ ~~h. Tamoxifen, estrogens or progestins unless on a stable dose for at least 4 months prior to screening and dose and regimen expected to remain constant during the treatment period~~ ~~i. Plasma apheresis within 4 weeks prior to screening or planned during the study~~ ~~j. Prior exposure to ISIS 304801~~ ~~k. Any other medication unless stable at least 4 weeks prior to screening (Occasional or intermittent use of over-the-counter medications will be allowed at Investigator's discretion)~~ ~~15. Blood donation of 50 to 499 mL within 30 days of screening or of > 499 mL within 60 days of screening~~ ~~16. Known hypersensitivity to any of the excipients of the Study Drug (ISIS 304801 or placebo)~~ ~~17. Have any other conditions, which, in the opinion of the Investigator or the Sponsor would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the study~~	To exclude enrollment of FCS patients in this open-label study who did not participate in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies.

Protocol Section	Description of Change	Rationale
Synopsis Study Design and Treatment Schema Section 3.1 Study Design Section 3.4.1 Qualification	The study for an individual patient will generally consist of the following periods: • ~~Group 1 and 2 patients (participated in ISIS 304801-CS6 or ISIS 304801-CS16 index study):~~ A qualification period of up to 2 weeks (unless approved by the Sponsor). Please refer to Section 4.1 and Appendix A • ~~Group 3 patients (did not participate in an index study): An up to 8-week screening and qualification period, including a diet stabilization period of at least 6 weeks (screening and diet stabilization period may be reduced, per Sponsor approval, if the patient is following a diet for optimal control of TGs and disease management prior to screening). Please refer to Section 6.1.2 and Appendix A~~ • ~~All patients:~~ ○ A 52-week treatment period during which volanesorsen will be administered as a once weekly SC injection ○ Option to participate in an extended treatment period (up to an additional 52 weeks) ○ A 13-week post-treatment evaluation period or expanded access program The patients, Investigators, study staff, and the Sponsor will remain blinded to lipid data through the last patient's Week 13 visit of the open-label study or until results from the database locks for the ISIS 304801-CS6 and ISIS 304801-CS16 index studies becomes available, whichever comes first. Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), adverse events (AE), concomitant medication/procedure information, lipid panel, blood viscosity, volanesorsen plasma concentrations, immunogenicity (IM) testing, platelet aggregation, liver/spleen magnetic resonance imaging (MRI), ECGs, echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Dietary counseling will be repeated at intervals throughout the treatment and follow-up period and a daily food/drink diary will be completed for the week prior to each quarterly visit by each patient. Following the Week 52 visit, patients will have the option of participating in an expanded access program or continuing dosing for up to an additional 52 weeks until an expanded access program is approved and available in their country. Patients not participating in an expanded access program will enter the 13-week post-treatment evaluation period.	To exclude enrollment of FCS patients in this open-label study who did not participate in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies. To allow patients who complete the 52-week treatment period to participate in an expanded access program or continue dosing for up to an additional 52 weeks until an expanded access program is approved and available in their country.
Section 3.4.3 Post-Treatment	The post-treatment evaluation period is 13 weeks and consists of ~~2~~7 Study Center visits on Weeks 53, 54, 55, 56, 57, 58, and 65 (Weeks 53, 54, 55, 56, 57, and 58 may be conducted by a home healthcare nurse).	To provide added patient safety regarding platelet count reductions and ISIS 304801 dose exposure.

Protocol Section	Description of Change	Rationale
Section 4.1 Qualification	~~Group 3 (Screening and Qualification): At the time of consent, the patient will be considered enrolled into the study and will be assigned a unique screening number before any study procedures, including screening procedures, are performed. At the time of enrollment, patients will be assigned a unique patient identification number. This number will be used to identify the patient throughout the trial and must be used on all study documentation related to that patient. The screening number and patient identification number must remain constant throughout the entire trial. In the event the patient is re-consented and re-screened the patient must be given a new screening number. Screening numbers and patient identification numbers, once assigned, will not be re-used.~~	To exclude enrollment of FCS patients in this open-label study who did not participate in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies.
Section 6.1 Study Schedule	~~6.1.2 Screening and Qualification (Group 3)~~ ~~Before any study specific procedures or evaluations are initiated, patients must sign and date the informed consent form. An 8-week period, including a diet stabilization period of at least 6 weeks (screening and diet stabilization period may be reduced, per Sponsor approval, if the patient is following a diet for optimal control of TGs and disease management prior to screening) is given to perform the screening evaluations. The qualification assessments will be performed at Week -2 to -1, ideally after patient eligibility has been determined, and on Study Day 1. Abnormal screening results may be retested for review by the Study Medical Monitor for eligibility purposes~~	To exclude enrollment of FCS patients in this open-label study who did not participate in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies.
Section 6.1.2 Treatment Period	During the treatment period, patients will report to the study center for clinic visits a minimum of 5 times during Weeks 1-52 (see Schedule of Procedures in Appendix A). Study Drug will be administered once weekly <u>unless the patient is on a biweekly dosing schedule for safety reasons</u> (Section 8.1). Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), AEs, concomitant medication/procedure information, lipid panel, <u>blood viscosity</u>, volanesorsen plasma concentrations, immunogenicity (IM) testing, <u>platelet aggregation</u>, liver/spleen MRI, ECGs, echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Adverse events at the injection site should be collected as adverse events. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period and all patients will complete a daily food diary for one week prior to their quarterly visit. All blood and urine samples should be collected prior to volanesorsen administration. Blood sampling at Weeks 2, 3, 4, 5, 6, <u>7</u>, 8, <u>9</u>, 10, <u>11</u>, 12, <u>14</u>, 15, <u>16</u>, 17, <u>18</u>, 19, <u>20</u>, 21, <u>22</u>, 23, <u>24</u>, 25, <u>27</u>, 28, <u>29</u>, 30, <u>31</u>, 32, <u>33</u>, 34, <u>35</u>, 36, <u>37, 39</u>, 40, <u>41</u>, 42, <u>43</u>, 44, <u>45</u>, 46, <u>47</u>, 48, <u>49, 50</u>, and ~~50~~<u>51</u> may be conducted by a home healthcare nurse. Approval for study procedures to be conducted by a home healthcare nurse on other outpatient visit days will require prior approval by the Sponsor. Patients must be fasted prior to drawing all blood samples and samples drawn locally should also be sent to the central laboratory for analysis whenever possible. ~~Every effort should be made to ensure the previous week's dose is given 7 days prior to a scheduled clinic visit.~~ Dosing instructions and training will be provided to the patient where applicable.	To provide added patient safety regarding platelet count reductions and ISIS 304801 dose exposure.

Protocol Section	Description of Change	Rationale
Section 6.1.3 Extended Treatment Period	6.1.3 Extended Treatment Period Patients will have the option of continuing dosing for up to an additional 52 weeks until an expanded access program is approved and available in their country. During the extended treatment period, patients will report to the study center for clinic visits during Weeks 54-104 (see Schedule of Procedures in Appendix A). Study Drug will be administered once weekly unless the patient is on a biweekly dosing schedule for safety reasons (Section 8.1). Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), AEs, concomitant medication/procedure information, lipid panel, volanesorsen plasma concentrations, IM testing, ECGs, and physical examinations will be performed according to the Schedule of Procedures in Appendix A. Adverse events at the injection site should be collected as adverse events. Dietary counseling will be reinforced at intervals throughout the extended treatment period. All blood and urine samples should be collected prior to volanesorsen administration. Blood sampling at Weeks 53, 54, 55, 56, 57, 58, 59, 60, 61, 62,63, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, and 103 may be conducted by a home healthcare nurse. Approval for study procedures to be conducted by a home healthcare nurse on other outpatient visit days will require prior approval by the Sponsor. Patients must be fasted prior to drawing all blood samples and samples drawn locally should also be sent to the central laboratory for analysis whenever possible. Dosing instructions and training will be provided to the patient where applicable.	To allow patients who complete the 52-week treatment period to participate in an expanded access program or continue dosing for up to an additional 52 weeks until an expanded access program is approved and available in their country.
Section 6.1.5 Post-Treatment Period	After completion of the Week 52 visit assessments, patients will have the option of participating in an expanded access program or continuing dosing for up to an additional 52 weeks until an expanded access program is approved and available in their country as described in Section 6.1.4. Patients not participating in an expanded access program will enter the 13-week post-treatment evaluation period. This 13-week post-treatment evaluation period consists of ~~4~~ 7 Study Center visits on Weeks 53, 54, 55, 56, 57, and 58 (which may be conducted by a home healthcare nurse), and Week 65 as outlined in the Schedule of Procedures in Appendix A. Patients who complete, or terminate early from, the extended treatment period without subsequently participating in an expanded access program will enter a 13-week post-treatment evaluation period consisting of 7 Study Center visits on Weeks 105, 106, 107, 108, 109, and 110 (which may be conducted by a home healthcare nurse), and Week 117 as outlined in the Schedule of Procedures in Appendix A.	To allow patients who complete the 52-week treatment period to participate in an expanded access program or continue dosing for up to an additional 52 weeks until an expanded access program is approved and available in their country. To provide added patient safety regarding platelet count reductions and ISIS 304801 dose exposure.

Protocol Section	Description of Change	Rationale
Section 6.2.1 Laboratory Assessments	Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1-week and ~~determined not to have met a stopping rule~~the result must be reviewed by the Investigator and confirmed to be acceptable before dosing can continue. ~~If there is no reportable platelet count within 14 days of the last platelet count, the Investigator will contact the patient to hold dosing until a new platelet count is obtained and reviewed.~~ All platelet count results will be promptly reviewed by the Investigator to ~~ensure that~~determine if the count has ~~not~~ met ~~the~~a stopping rule, or the dose reduction rule ~~and to determine whether the rate of decline is suggestive that the patient could be approaching~~of 100,000/mm^3, or the dose pause rule of 75,000/mm^3. Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor.	To provide added patient safety regarding platelet count reductions, ISIS 304801 dose exposure, and treatment recommendations.
Section 6.2.4 ECG	The ECG will be recorded after the patient has been resting in a supine position for at least 5 minutes. ECGs will be performed in triplicate at Week 13, Week 26, Week 38, Week 52, and Week 65. Patients in the Extended Treatment Period will have ECGs performed in triplicate at Week 76 and Week 104.	To provide patient safety during the Extended Treatment Period.
Section 6.2.8 Diet Monitoring	2. Patients will receive diet/alcohol counseling by qualified study personnel at clinic visits throughout the course of the study. Qualified study personnel will telephone the patient to provide diet/alcohol counseling for visits that are conducted by a clinical service. Patients in the Extended Treatment Period will receive diet/alcohol counseling by qualified study personnel at clinic visits only. 3. In addition to the 7-day food diary and the diet /alcohol counseling during clinic visits, telephone calls from a dietitian or qualified study personnel to assess as to how each patient is maintaining their diet ~~will~~ may be conducted randomly during the treatment and post treatment follow-up periods.	To provide diet/alcohol counseling during the Extended Treatment Period.
Section 6.2.10 Chart Review for Incidents of Acute Pancreatitis in Medical History (Group 2)	6.2.10 Chart Review for Incidents of Acute Pancreatitis in Medical History (Group 2) Patient records will be reviewed for incidents of acute pancreatitis occurring up to 5 years prior to Qualification and information relating to these events will be collected for independent adjudication.	To assess acute pancreatitis in medical history in Group 2 patients.
Section 8.1 Volanesorsen Administration	~~Every effort should be made to ensure the previous week's dose is given 7 days prior to a scheduled clinic visit.~~	Dosing recommendations provided in updated monitoring and drug administration updates.

Protocol Section	Description of Change	Rationale
Section 8.5.2 Safety Monitoring for Platelet Count Results	Actions to be taken in the event of reduced platelet count are shown in Table ~~2~~3 in Section 8.6.3. Monitor every 1 week unless otherwise specified. Study Drug administration is contingent on the availability of the immediately preceding test result. An interpretable platelet value must be available within 7 days prior to dosing. Only the study doctor or qualified designee can authorize continued Study Drug administration based on an acceptable platelet value. Patients should not administer a dose until they have been contacted by their study doctor or designee and told that it is acceptable to dose. Authorization to dose must be documented in the patient's medical records. Due to the 1 to 2-year study duration it is anticipated that patients may undertake travel including vacations, which may impede weekly platelet monitoring. In some situations, it may be possible to arrange for local laboratory testing or use of the home healthcare service at their temporary location. The intent is to maintain weekly platelet monitoring and dosing where possible, as well as Investigator site contact with the study patients. However, if the above options are not possible, a temporary interruption of study treatment will be planned with a prompt blood draw upon the patient's return which must be reported and reviewed by the Investigator prior to the patient resuming dosing. The tests outlined in Table 2 should also be performed as soon as possible. Additional lab tests will be determined by the Sponsor Medical Monitor or designee in consultation with the Investigator. Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor (See also Stopping Rules Section 8.6.3).	To provide added patient safety regarding platelet count reductions, ISIS 304801 dose exposure, and treatment recommendations.

<table>
<tr><th>Protocol Section</th><th>Description of Change</th><th>Rationale</th></tr>
<tr><td>Section 8.5.2 Safety Monitoring for Platelet Count Results
Continued</td><td>Added Table 2:
Table 2 Labs to Be Performed in the Event of a Platelet Count Less than the Lower Limit of Normal (x2) or < 100,000/mm^3 (x1)*
*In patients who have any 2 occurrences (consecutive or non-consecutive) of platelet count less than the lower limit of normal or who have any 1 occurrence of platelets < 100,000/mm^3. Labs only need to be performed once. Labs may be collected over multiple visits, if blood requirements are a concern, as per investigator discretion.
Note: The following labs may change as additional data is assessed, and sites will be updated regarding any changes.
<table>
<tr><td>To Be Performed at Local Lab</td></tr>
<tr><td>Peripheral smear (should be performed locally, fixed and sent to central lab for review)</td></tr>
<tr><td>Fibrinogen split products or D-dimer on fresh blood</td></tr>
<tr><td>To Be Performed at Central Lab</td></tr>
<tr><td>Citrated sample for platelets</td></tr>
<tr><td>Coagulation panel (PT/INR, aPTT)</td></tr>
<tr><td>CBC with reticulocytes</td></tr>
<tr><td><u>Folate (folic acid)</u></td></tr>
<tr><td><u>Vitamin B12</u></td></tr>
<tr><td>Fibrinogen</td></tr>
<tr><td>von Willebrand factor</td></tr>
<tr><td>Total globulins, total IgA, IgG and IgM</td></tr>
<tr><td>Complement: total C3, total C4, Bb, C5a</td></tr>
<tr><td>hsCRP</td></tr>
<tr><td><u>Helicobacter pylori (breath test)</u></td></tr>
<tr><td>Serology for:</td></tr>
<tr><td>HBV, HCV, HIV (if not done recently for Qualification)</td></tr>
<tr><td>Rubella</td></tr>
<tr><td>CMV</td></tr>
<tr><td>EBV</td></tr>
<tr><td>Parvo B19</td></tr>
<tr><td><s>Helicobacter pylori (IgG serum test)</s></td></tr>
<tr><td>Auto-antibody screen:</td></tr>
<tr><td>Antiphospholipid</td></tr>
<tr><td>Rheumatoid factor</td></tr>
<tr><td>Anti-dsDNA</td></tr>
<tr><td>Anti-thyroid</td></tr>
<tr><td>To Be Performed at Specialty Lab(s)</td></tr>
<tr><td>Antiplatelet antibodies and Anti-PF4 assay</td></tr>
<tr><td>Anti-ASO antibody</td></tr>
</table></td><td>To provide added patient safety regarding platelet count reductions, ISIS 304801 dose exposure, and treatment recommendations.</td></tr>
</table>

Protocol Section	Description of Change	Rationale
Section 8.6.3 Stopping Rules for Platelet Count Results	Actions to be taken in the event of a low platelet count are summarized in Table ~~2~~3 below. In the event of a platelet count less than 75,000/mm^3 that is associated with major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with volanesorsen will be stopped permanently. The follow-up schedule for any events meeting this stopping criterion will be determined by the Investigator in consultation with the Sponsor Medical Monitor. In the event of any platelet count less than ~~25~~50,000/mm^3, or a platelet count less than 75,000/mm^3 that occurs while the patient is on dosing at 300 mg every 2 weeks ~~or 150 mg every week~~ then dosing of a patient with volanesorsen will be stopped permanently. Platelet count will be monitored as outlined in Table 3. ~~daily until 2 successive values show improvement then monitored every 2-3 days until platelet count is stable.~~ Administration of steroids is recommended for patients whose platelet count is less than ~~25~~50,000/mm^3. Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5 2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (note: may require continuation with oral steroids after methylprednisolone). Triglyceride levels be monitored weekly, and AE monitoring will continue, during corticosteroid treatment and the laboratory alert will be changed from an increase of 2,000 to 500 mg/dL during that period. In the event of a platelet count less than 75,000/mm^3, and in the absence of major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with volanesorsen should be suspended temporarily until the platelet count has recovered to > 100,000/mm^3. If dosing is continued it should be at a reduced dose frequency of 300 mg every 2 weeks ~~or a reduced dose of 150 mg per week~~ (refer to Section 8.7). The suitability of the patient for continued dosing will be determined by the Investigator in consultation with the Study Medical Monitor and will be based on factors such as the original rate of decline in the patient's platelet count, whether any bleeding events were experienced by the patient, and the speed of recovery of platelet count upon holding of dosing. If after the first dosing rechallenge the platelet count again falls below 75,000/mm^3, then dosing of the patient with Study Drug will be stopped permanently. ~~Following a rechallenge platelet count should be tested every week until count is stable.~~ ~~Any unreportable platelet count result must be rechecked and determined not to have met a stopping rule before dosing can continue.~~ ~~If there is no reportable platelet count within 14 days of the last platelet count, the Investigator will contact the patient to hold dosing until a new platelet count is obtained and reviewed.~~	To provide added patient safety regarding platelet count reductions, ISIS 304801 dose exposure, and treatment recommendations.

<table>
<tr><th>Protocol Section</th><th>Description of Change</th><th>Rationale</th></tr>
<tr><td>Section 8.6.3 Stopping Rules for Platelet Count Results Continued</td><td>Was:
Table 2 Actions in Patients with Low Platelet Count
<table>
<tr><th>Platelet Count on Rx</th><th>Drug Dose</th><th>Monitoring</th></tr>
<tr><td>Normal range, > 140K/mm^3</td><td>No action</td><td>Monitor every 2 weeks</td></tr>
<tr><td>100K-140K/mm^3</td><td>No action</td><td>Closer observation
Monitor every 1 week until stable*</td></tr>
<tr><td>75K-100K/mm^3</td><td>Permanently reduce dose frequency to 300 mg every 2 weeks or reduce dose to 150 mg weekly</td><td>Closer observation
Monitor every 1 week</td></tr>
<tr><td>50K-75K/mm^3</td><td>If occurs while on dose of 300 mg every 2 weeks or 150 mg every week then permanently discontinue Study Drug, otherwise dose pause.
When platelet count returns to > 100K/mm^3 restart dosing at dose frequency of 300 mg every 2 weeks or 150 mg weekly only if approved by Sponsor Medical Monitor</td><td>Closer observation
Monitor every 2-3 days until 2 successive values show improvement
Consider discontinuation of antiplatelet agents/NSAIDS/ anticoagulant medication</td></tr>
<tr><td>25K-50K/mm^3</td><td>If occurs while on dose of 300 mg every 2 weeks or 150 mg every week then permanently discontinue Study Drug, otherwise dose pause.
When platelet count returns to > 100K/mm^3 restart dosing at dose frequency of 300 mg every 2 weeks or 150 mg weekly only if approved by Sponsor Medical Monitor</td><td>Closer observation
Monitor daily until 2 successive values show improvement then monitor every 2-3 days until platelet count stable
Discontinue antiplatelet agents/NSAIDS/anticoagulant medication while platelet count < 50K/mm^3 if possible</td></tr>
</table></td><td>To provide added patient safety regarding platelet count reductions, ISIS 304801 dose exposure, and treatment recommendations.</td></tr>
</table>

<table>
<tr><th>Protocol Section</th><th>Description of Change</th><th>Rationale</th></tr>
<tr><td>Section 8.6.3 Stopping Rules for Platelet Count Results Continued</td><td>
Table 2 Actions in Patients with Low Platelet Count Continued
<table>
<tr><th>Platelet Count on Rx</th><th>Drug Dose</th><th>Monitoring</th></tr>
<tr><td>< 25K/mm^3</td><td>Permanently discontinue Study Drug</td><td>Closer observation:
Monitor daily until 2 successive values show improvement then monitor every 2-3 days until platelet count stable
Steroids recommended**
Consider need for hospitalization and referral to hematologist
Discontinue antiplatelet agents/NSAIDS/anticoagulant medication while platelet count < 50K/mm^3 if possible</td></tr>
</table>
* At least 3 consecutive values measured weekly that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3
** Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (note: may require continuation with oral steroids after methyl prednisolone)
</td><td>To provide added patient safety regarding platelet count reductions, ISIS 304801 dose exposure, and treatment recommendations.</td></tr>
</table>

<table>
<tr><th>Protocol Section</th><th>Description of Change</th><th>Rationale</th></tr>
<tr><td>Section 8.6.3 Stopping Rules for Platelet Count Results
Continued</td><td>Is:

Table 3 Actions in Patients with Low Platelet Count or Drop in Platelet Count
<table>
<tr><th>Platelet Count on Rx</th><th>Drug Dose</th><th>Monitoring</th></tr>
<tr><td></td><td>Study Drug administration is contingent on the availability of the immediately preceding test result. An interpretable platelet value must be available within 7 days prior to dosing. Only the study doctor or qualified designee can authorize continued Study Drug administration based on an acceptable platelet value. Patients should not administer a dose until they have been contacted by their study doctor or designee and told that it is acceptable to dose. Authorization to dose must be documented in the patient's medical records.</td><td>Monitor every 1 week unless otherwise specified
Obtain additional lab tests (Table 2) if 2 occurrences consecutive or non-consecutive) of platelet count 140K - > 100K/mm^3 or 1 occurrence of platelet count ≤ 100K/mm^3. Labs only need to be performed once. Labs may be collected over multiple visits, if blood requirements are a concern, as per Investigator discretion.</td></tr>
<tr><td>> 100K/mm^3</td><td>Weekly 300 mg Study Drug administration</td><td></td></tr>
<tr><td>100K/mm^3 - > 75K/mm^3</td><td>Permanently reduce dose frequency to 300 mg every 2 weeks</td><td></td></tr>
<tr><td>75K/mm^3 - > 50K/mm^3</td><td>• If occurs while on dose of 300 mg every 2 weeks then permanently discontinue Study Drug, otherwise dose pause
• When platelet count returns to > 100K/mm^3 restart dosing at dose frequency of 300 mg every 2 weeks only if approved by Sponsor Medical Monitor</td><td>• Monitor every 2-3 days until 2 successive values are >75K/mm^3 then monitor every 1 week
• Consider discontinuation of antiplatelet agents/NSAIDS/ anticoagulant medication</td></tr>
</table></td><td>To provide added patient safety regarding platelet count reductions, ISIS 304801 dose exposure, and treatment recommendations.</td></tr>
</table>

<table>
<tr><th>Protocol Section</th><th>Description of Change</th><th>Rationale</th></tr>
<tr><td>Section 8.6.3 Stopping Rules for Platelet Count Results Continued</td><td>Table 3 Actions in Patients with Low Platelet Count or Drop in Platelet Count Continued
<table>
<tr><th>Platelet Count on Rx</th><th>Drug Dose</th><th>Monitoring</th></tr>
<tr><td>≤ 50K/mm^3</td><td>Permanently discontinue Study Drug</td><td>• Monitor daily until 2 successive values show improvement then monitor every 2-3 days until 2 successive values are > 75K/mm^3 then monitor every 1 week
• Patient should be evaluated by a hematologist to provide diagnostic and therapeutic management
• Steroids recommended*. It is strongly recommended that, unless the patient has a medical contraindication to receiving glucocorticoids, the patient receives glucocorticoid therapy to reverse the platelet decline.
• Monitor triglyceride levels weekly and continue AE monitoring during steroid therapy
• Discontinue antiplatelet agents/ NSAIDS/ anticoagulant medication while platelet count is< 50K/mm^3 if possible</td></tr>
</table>
* Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or methylprednisolone 30 mg/kg/day for 7 days (note: may require continuation with oral steroids after methylprednisolone)</td><td>To provide added patient safety regarding platelet count reductions, ISIS 304801 dose exposure, and treatment recommendations.</td></tr>
</table>

Protocol Section	Description of Change	Rationale
Synopsis Section 10.1.1 Efficacy Endpoints	• Percent change and absolute change from baseline in fasting TG • Frequency and severity of patient reported abdominal pain during the treatment period • Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-HDL-C, apoB, HDL-C, apolipoprotein A-1 (apoA-1), VLDL-C, and LDL-C • Percent change from baseline in fasting total apolipoprotein C-III • Change in blood viscosity (may be evaluated) • Quality of Life questionnaires (EQ-5D, SF-36) • Adjudicated acute pancreatitis event rate • Other symptoms: eruptive xanthoma, lipemia retinalis	Blood viscosity added to assess potential benefit of ISIS 304801 administration.
Synopsis Section 10.1.2 Safety Endpoints	• Adverse events including adjudicated events of pancreatitis and MACE • Vital signs and weight • Physical examinations • Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis) • Echocardiography • Electrocardiograms (ECGs) • Use of concomitant medications • MRIs • Platelet aggregation (may be evaluated)	Platelet aggregation added to assess platelet function following ISIS 304801 administration.
Section 10.3 Populations	Full Analysis Set (FAS): All patients who are enrolled and received at least 1 dose of active Study Drug and have a baseline TG assessment. The FAS represents the practically-feasible intent-to-treat (ITT) population as delineated in ICH Guideline E9. Per Protocol Set (PPS): Subset of the FAS who received 9 of first 13 scheduled doses of volanesorsen and with no significant protocol deviations that would be expected to affect efficacy and PD assessments. The detailed criteria will be specified and finalized prior to the final database lock. Safety Set: All patients who are enrolled and receive at least 1 dose of volanesorsen. PK Population: All patients who are enrolled, receive at least 1 dose of volanesorsen, and have at least 1 ~~evaluable~~ post first dose PK sample collected, analyzed, and reported.	Modified to include, in the FAS, only those patients that are randomized and dosed and have a baseline TG assessment and clarified the PK Population.
Section 10.4 Definition of Baseline	Definitions of baseline are given below for the purposes of the final analysis. For fasting lipid measurements, 2 baselines are defined for each patient in Groups 1 and 2: Group 1 (ISIS 304801-CS6) or Group 2 (ISIS 304801-CS16) index study baseline and the baseline in this open-label study, which is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 (e.g., qualification assessments or assessments from final visit of the ISIS 304801-CS6 or ISIS 304801-CS16 index studies if used for qualification). ~~For Group 3 patients, the baseline for fasting lipid measurements is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 in this open-label study.~~ For other measurements, baseline for patients on active treatment in the ISIS 304801-CS6 or ISIS 304801-CS16 index study will be the ISIS 304801-CS6 or ISIS 304801-CS16 index study baseline. For patients on placebo in the ISIS 304801-CS6 or ISIS 304801-CS16 index study ~~and Group 3 patients~~, baseline will be the last non-missing assessment prior to the first dose of Study Drug.	To exclude enrollment of FCS patients in this open-label study who did not participate in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies.

Protocol Section	Description of Change	Rationale
Appendix A	Removed Screening period (Group 3) Removed Week 2.5 **Added:** Medical History b Patient charts will be reviewed in order to collect data for events of acute pancreatitis or suspected pancreatitis in the patient's medical history. Chart review may be conducted at any time during the study. These events will be adjudicated in the same manner as for events of pancreatitis during the study CBC with Differential c Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1 week and the result must be reviewed by the Investigator and confirmed to be acceptable ~~and determined not to have met a stopping rule~~ before dosing can continue~~. If there is no reportable platelet count within 14 days of the last platelet count, the Investigator will contact the patient to hold dosing until a new platelet count is obtained and reviewed~~. All platelet count results will be promptly reviewed by the Investigator to ~~ensure that~~ determine if the count has ~~not~~ met ~~the~~ a stopping rule, ~~and to determine whether the rate of decline is suggestive that the patient could be approaching the~~ or the dose reduction rule of 100,000/mm^3, or the dose pause rule of 75,000/mm^3. Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor **Added:** Troponin I **Added:** Blood Viscosity, Platelet Aggregation, Platelet Bound Autoantibodies e May be done. Blood viscosity and platelet aggregation in volanesorsen-treatment naïve patients only **Added:** archive blood sample for potential gene sequencing related to hypertriglyceridemia (Group 2 if not available from index study)	Added troponin, platelet bound autoantibodies, and modified CBC blood draws to provide added patient safety regarding platelet count reductions, ISIS 304801 dose exposure, and treatment recommendations. Added patient chart review, blood viscosity and potential gene sequencing to assess potential benefit of ISIS 304801 administration. Added platelet aggregation to assess platelet function following ISIS 304801 administration.
Appendix A	**Added:** Appendix A Schedule of Procedures – Extended Treatment Period Table and Legend.	To allow patients who complete the 52-week treatment period to participate in an expanded access program or continue dosing for up to an additional 52 weeks until an expanded access program is approved and available in their country.

Protocol Section	Description of Change	Rationale
Appendix B	Removed Screening Tests (Group 3) **Added**: Troponin I[2] CK-MB[2] Platelet Bound Autoantibodies[3] Blood Viscosity[3] Platelet Aggregation[3] 2 All abnormal troponin samples will be rerun at the central laboratory and also analyzed for CK-MB 3 May be done	Added troponin, CK-MB, and platelet bound autoantibodies, provide added patient safety. Added Blood Viscosity to assess potential benefit of ISIS 304801 administration Added Platelet Aggregation to assess platelet function following ISIS 304801 administration.
Appendix C	**Added:** Appendix C PK Sampling Schedule (Extended Treatment Period) Table.	To collect intermittent PK data in patients who enter the extended treatment period.

PROTOCOL SYNOPSIS

Protocol Title	An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Study Phase	3
Indication	Familial Chylomicronemia Syndrome
Study Objectives	To evaluate the safety and efficacy of dosing and extended dosing with volanesorsen (volanesorsen sodium 300 mg) in patients with FCS
Study Design	This is a multi-center open-label study of: Group 1: ISIS 304801-CS6 (index study) roll-over FCS patients Group 2: ISIS 304801-CS16 (index study) roll-over FCS patients All patients will receive volanesorsen 300 mg once per week for 52 weeks. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period. Following the Week 52 visit, patients will have the option of participating in an expanded access program or continuing dosing for up to an additional 52 weeks until an expanded access program is approved and available in their country. Patients not participating in an expanded access program will enter a 13-week post-treatment evaluation period
Number of Patients	Up to approximately 70 patients dosed
Study Population	Inclusion Criteria: 1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law 2. Age ≥ 18 years at time of informed consent 3. Groups 1 and 2: Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement. Group 2: Patients who enrolled in ISIS 304801-CS16 must also meet the following criteria in order to enter into the open-label study: a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L) b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) supported by documentation of at least 1 of the following: • Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1) • Post heparin plasma LPL activity of ≤20% of normal in medical history. Note: testing of LPL activity should not be performed to confirm eligibility for the study c. Group 2: Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Qualification for the ISIS 304801-CS16 index study 4. Able and willing to participate in a 65-week study

PROTOCOL SYNOPSIS Continued

Study Population *Continued*	Inclusion Criteria: *Continued* 5. Satisfy 1 of the following: a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved), abstinent*, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration b. Males: Surgically sterile, abstinent* or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration * Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception Exclusion Criteria for Group 1 (ISIS 304801-CS6) and Group 2 (ISIS 304801-CS16) Index Study Roll-over Patients 1. Have any new condition or worsening of existing condition which in the opinion of the Investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study 2. Unwilling to comply with lifestyle requirements for the duration of the study (Section 6.3)
Treatment Group	Volanesorsen 300 mg once per week
Study Drug Administration	Volanesorsen will be administered as subcutaneous (SC) injections.
Dose Adjustments	Dose adjustments, including dose interruptions and/or decreasing the dose frequency will be allowed for safety or tolerability after consultation with the Sponsor Medical Monitor.
Rationale for Dose and Schedule Selection	The dose of 300 mg once weekly was chosen for the double-blinded placebo-controlled Phase 3 index studies (ISIS 304801-CS6 and ISIS 304801-CS16) based on the pharmacodynamic and safety analysis of the Phase 2 studies (Section 2.4) which included a subset of patients with FCS. The same dose of 300 mg once weekly will be used in this open-label study of FCS patients.

PROTOCOL SYNOPSIS *Continued*

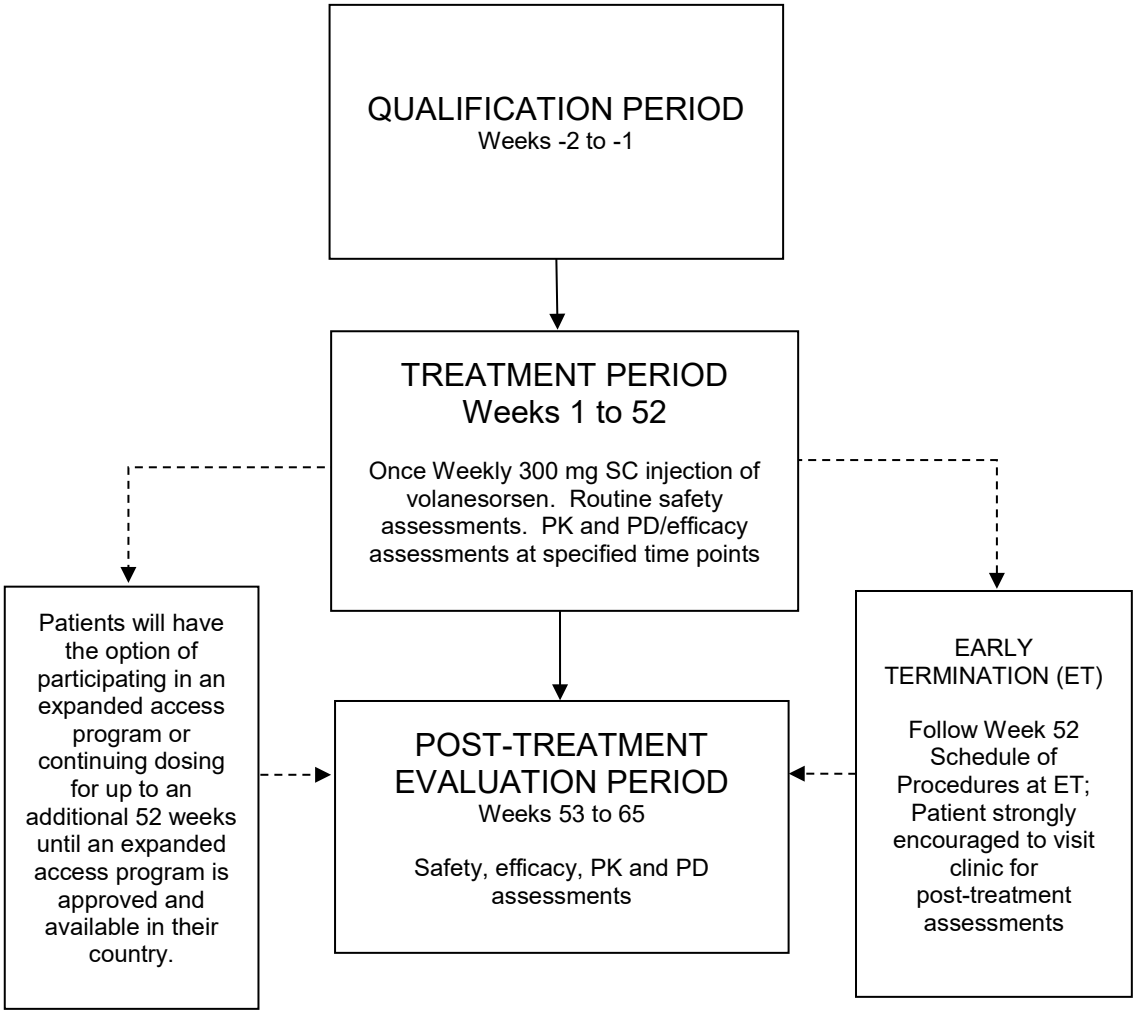
Study Visit Schedule and Procedures	The study for an individual patient will generally consist of the following periods:
	• A qualification period of up to 2 weeks (unless approved by the Sponsor). Please refer to Section 4.1 and Appendix A
	  ○ A 52-week treatment period during which volanesorsen will be administered as a once weekly SC injection
	  ○ Option to participate in an extended treatment period (up to an additional 52 weeks)
	  ○ A 13-week post-treatment evaluation period or expanded access program
	The patients, Investigators, study staff, and the Sponsor will remain blinded to lipid data through the last patient's Week 13 visit of the open-label study or until results from the database locks for the ISIS 304801-CS6 and ISIS 304801-CS16 index studies becomes available, whichever comes first.
	Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), adverse events (AE), concomitant medication/procedure information, lipid panel, blood viscosity, volanesorsen plasma concentrations, immunogenicity (IM) testing, platelet aggregation, liver/spleen magnetic resonance imaging (MRI), ECGs, echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Dietary counseling will be repeated at intervals throughout the treatment and follow-up period and a daily food/drink diary will be completed for the week prior to each quarterly visit by each patient. Following the Week 52 visit, patients will have the option of participating in an expanded access program or continuing dosing for up to an additional 52 weeks until an expanded access program is approved and available in their country. Patients not participating in an expanded access program will enter the 13-week post-treatment evaluation period.

Safety and Tolerability Evaluations	Overall safety and tolerability of volanesorsen will be assessed by determining the incidence and severity of adverse and serious adverse events (including independently adjudicated events of acute pancreatitis and MACE), withdrawals due to adverse events, and changes in laboratory and other safety parameters.

PROTOCOL SYNOPSIS *Continued*

Planned Analyses	Safety Endpoints: • Adverse events including adjudicated events of acute pancreatitis and MACE • Vital signs and weight • Physical examinations • Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis) • Echocardiography • Electrocardiograms (ECGs) • Use of concomitant medications • MRIs • Platelet aggregation (may be evaluated) Efficacy Endpoints: • Percent change and absolute change from baseline in fasting TG • Frequency and severity of patient reported abdominal pain during the treatment period • Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-high-density lipoprotein-cholesterol (non-HDL-C), apolipoprotein B [apoB], high-density lipoprotein-cholesterol (HDL-C), apolipoprotein A-1 [apoA-1], very-low-density lipoprotein-cholesterol (VLDL-C), and LDL-C • Percent change from baseline in fasting total apolipoprotein C-III (apoC-III) • Change in blood viscosity (may be evaluated) • Quality of Life questionnaires (EQ-5D, SF-36) • Adjudicated acute pancreatitis event rate • Other symptoms: eruptive xanthoma, lipemia retinalis
Pharmacokinetic Evaluations	Plasma samples will be taken from all patients for the measurement of volanesorsen as follows: trough levels (pre-dose) throughout treatment and post-treatment levels during the post-treatment follow-up period. In a subset of patients, more frequent assessment of plasma concentrations of volanesorsen will be performed to determine volanesorsen pharmacokinetic parameters. Plasma sample collection time points are detailed in Appendix A and Appendix C.
Statistical Considerations	No sample size calculations were performed as this is an open-label study.
Sponsor	Ionis Pharmaceuticals, Inc.
Collaborator	Akcea Therapeutics

STUDY DESIGN AND TREATMENT SCHEMA



STUDY GLOSSARY

Abbreviation/Acronym	Definition
ADA	anti-drug antibody
AE	adverse Event
ALP	alkaline Phosphatase
ALT	alanine Aminotransferase
ANA	antinuclear Antibody
apoA-1	apolipoprotein A-1
apoB	apolipoprotein B
apoC-III	apolipoprotein C-III
apoE	apolipoprotein E
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
CBC	complete blood count
C_{max}	maximum observed drug concentration
CRF	case report form
DNA	deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
ET	early termination
FAS	full analysis set
FCS	Familial Chylomicronemia Syndrome
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
GPIHBP1	glycosylphosphatidylinositol-anchored hdl-binding protein 1
HAPI	heritability and phenotype intervention
HbA1c	glycated hemoglobin
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein-cholesterol
hsCRP	High-sensitivity C-reactive protein
ICH	International Conference on Harmonization
IDL	intermediate density lipoprotein
IEC	Independent Ethics Committee
IM	immunogenicity
Index Studies	ISIS 304801-CS6 and ISIS 304801-CS16

INR	International Normalized Ratio
IRB	Institutional Review Board
IXRS	Interactive Voice/Web-Response System
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein-cholesterol
LMF1	lipase maturation factor 1
LPL	lipoprotein lipase
MACE	major acute cardiovascular event
MOE	2′-*O*-(2-methoxyethyl)
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NCS	not clinically-significant
NOAEL	no-observed-adverse-effect level
non-HDL-C	non-high-density lipoprotein-cholesterol
OTC	over the counter
PFS	prefilled syringe
PD	pharmacodynamic
PK	pharmacokinetic
PPS	per protocol set
PT	prothrombin time
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SUSAR	suspected unexpected serious adverse reaction
T2DM	type 2 diabetes mellitus
T_{max}	time to maximal concentration
TG	triglycerides
Treatment-emergent	occurring after first dose of Study Drug
TRL	triglyceride-rich lipoproteins
ULN	upper limit of normal
VLDL	very-low-density lipoprotein
VLDL-C	very-low-density lipoprotein-cholesterol
VLDL-TG	lipoprotein-triglyceride
WMA	World Medical Association

1. OBJECTIVES

The objective of the study is to evaluate the safety and efficacy of dosing and extended dosing with volanesorsen in patients with familial chylomicronemia syndrome.

2. BACKGROUND AND RATIONALE

2.1 Overview of Disease

Familial Chylomicronemia Syndrome (FCS) is an inherited disease characterized by severe hypertriglyceridemia and chylomicronemia, and risk or history of pancreatitis. It is a rare autosomal recessive disease that can be diagnosed either in childhood or adulthood.

Fasting plasma triglyceride (TG) levels in FCS patients are typically 10-fold to 100-fold above normal (1,500 to 15,000 mg/dL), despite extreme dietary fat restriction (20 g or approximately 15-20% of daily calorie intake) (Brunzell 1999-2011). Patients with FCS often present in infancy or childhood with frequent and severe abdominal pain, repetitive colicky pain, repeated episodes of potentially fatal acute pancreatitis, and failure to thrive (Brunzell 1999-2011; Tremblay et al. 2011). Physical examination frequently reveals eruptive xanthomas, lipemia retinalis and hepatosplenomegaly, and plasma from patients appears lactescent, interfering with determination of other laboratory parameters (Tremblay et al. 2011).

Patients with fasting triglyceride levels > 10 mmol/L probably have a component of chylomicronemia. Clinical diagnosis would include evidence of clinical features of chylomicronemia syndrome and secondary causes such as uncontrolled type 1 or type 2 diabetes mellitus (T2DM), hypothyroidism, poor diet, alcohol use, nephrotic syndrome or use of associated medications should be ruled out. The diagnosis of FCS may be made more specifically by genotyping or confirmation of very low or absent lipoprotein lipase (LPL) enzyme activity in post heparin plasma (Brunzell 1999-2011).

Patients with FCS carry a heavy burden of medical complications, the most serious, as described above, being an extreme risk of recurrent and potentially fatal pancreatitis. Due to the recurrent episodes of acute pancreatitis, these patients may also develop chronic pancreatitis and signs of exocrine or endocrine pancreatic insufficiency, including diabetes mellitus (Gaudet et al. 2013). While the pathophysiology underlying chylomicron-related pancreatitis has not been completely elucidated, 1 hypothesis is that large chylomicrons lodged in pancreatic capillaries are exposed to pancreatic lipase, with the subsequent release of free fatty acids through the hydrolysis of chylomicron-associated TGs. High concentrations of free fatty acids are thought to damage pancreatic cells leading to emergent pancreatitis (Yang et al. 2009; Berglund et al. 2012).

The etiology of extreme hypertriglyceridemia in FCS is considered to be ineffective triglyceride clearance, due to an extremely low level of LPL activity. LPL normally functions to hydrolyze triglycerides (TG) in chylomicrons along the luminal surface of capillaries, mainly in heart, skeletal muscle, and adipose tissue, promoting triglyceride clearance from the circulation. LPL is regulated by a number of key genes, and loss-of-function mutations in one of these genes, or the LPL gene itself, results in FCS (Surendran et al. 2012). In addition to loss of function mutations, null mutations, and nonsense mutations in the LPL gene, other genes currently identified in FCS patients, and known to directly influence LPL activity include: apolipoprotein C-II (APOC2) a cofactor for LPL (Schuster et al. 2011); apolipoprotein A-V

(APOA5) an enhancer of LPL activity (Schaap et al. 2004); lipase maturation Factor 1 (LMF1), a transmembrane protein involved in LPL maturation (Doolittle et al. 2009); glycosylphosphatidylinositol-anchored HDL-binding protein 1 (GPIHBP1), a capillary endothelial cell protein that provides a platform for LPL-mediated processing of chylomicrons (Beigneux et al. 2007).

2.2 Therapeutic Rationale

Apolipoprotein C-III (ApoC-III), a key regulator of plasma triglyceride levels, is a 79 amino acid glycoprotein synthesized principally in the liver (Ooi et al. 2008; Figure 1). ApoC-III is a major regulator of lipoprotein metabolism and plays a pivotal role in regulating plasma TG levels (Chan et al. 2008). It is a component of triglyceride-rich lipoproteins (TRLs) and a potent inhibitor of LPL (Lemieux et al. 2003). At higher concentrations apoC-III also inhibits hepatic lipase activity (Kinnunen and Ehnolm 1976), an enzyme which plays an important role in the conversion of dense very-low-density lipoprotein (VLDL) to intermediate density lipoprotein (IDL) and to LDL (Mendivil et al. 2010), as well as in the remodeling of HDL (Brown et al. 2010). In addition, increased apoC-III content adversely affects apoE-mediated hepatic uptake of TG-rich remnants (Mann et al. 1997). Thus, elevated plasma apoC-III levels are associated with impaired hydrolysis and retarded clearance of TG-rich particles, resulting in the accumulation of lipoprotein-triglyceride (VLDL-TG) and chylomicrons in plasma and the development of hypertriglyceridemia (Ito et al. 1990).

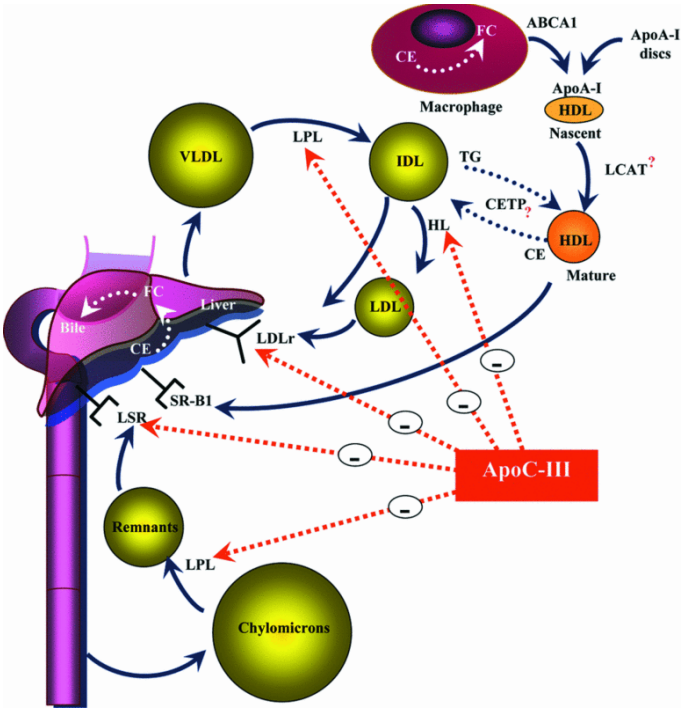


Figure 1 ApoC-III Regulates Lipoprotein Metabolism by Multiple Mechanisms

From Ooi et al. 2008; ABCA1 = ATP-binding cassette A1, apo = apolipoprotein, CE = cholesterol ester, CETP = cholesterol ester transfer protein, FC = free cholesterol, HDL = high-density lipoprotein, HL = hepatic lipase, IDL = intermediate-density lipoprotein, LCAT = lecithin cholesterol acyltransferase, LDL = low-density lipoprotein, LDLr = LDL receptor, LPL = lipoprotein lipase, LSR = lipolysis-stimulated receptor, SR-B1 = scavenger receptor B-1, TG = triglyceride, VLDL = very low-density lipoprotein.

Mechanistically, FCS is primarily a consequence of ineffective clearance of TRL. ApoC-III is a prominent component of TRL (e.g., VLDL and chylomicrons). In addition to its role in inhibiting LPL, apoC-III inhibits TRL remnant (TG-depleted remnant lipoprotein) uptake by hepatic lipoprotein receptors by steric inhibition of the interaction of apoE with these receptors.

Human genetic data have demonstrated positive phenotypic associations with loss (e.g., null or nonsense mutations) and negative effects with gain of function mutations (Atzmon et al. 2006; Pollin et al. 2008; Petersen et al. 2010). A novel nonsense mutation in the apoC-III gene was identified in the heritability and phenotype intervention (HAPI) heart study in Old Order Amish that results in lower plasma apoC-III and TG levels and lower LDL-C, increased HDL-C and reduced atherosclerosis (Pollin et al. 2008). In another study involving a group of 214 Ashkenazi Jews of advanced age (had passed or nearly reached 100 years of age), genotype analysis revealed a polymorphism in the apoC-III gene (APOC3-641CC genotype) with a clear pattern of age-dependent frequency that was associated with significantly lower levels of apoC-III protein, a favorable lipoprotein profile and increased longevity (Atzmon et al. 2006). In contrast to the Amish and Ashkenazi apoC-III polymorphisms associated with lower plasma TG, apoC-III polymorphisms associated with higher plasma TG have also been recently described (Petersen et al. 2010). In a cohort of lean (mean body mass index [BMI] = 24.7 ± 3.6 kg/m^2) Asian Indians, carriers of apoC-III variant alleles (C-482T, T-455C, or both) were noted to have significantly higher plasma apoC-III and TG levels, and decreased ability to clear postprandial plasma TG from the circulation. Taken together, the available data strongly support the development of a therapy that reduces plasma apoC-III levels in order to reduce the very high circulating triglyceride and chylomicron levels that are accompanied by increasing risk for acute pancreatitis.

Given the profound reductions in TGs observed with volanesorsen treatment in FCS patients who have no detectable LPL activity (See Section 2.3.4), and the mechanistic data available to date on apoC-III function, potential mechanisms that explain how apoC-III inhibition results in triglyceride reduction in FCS patients include: (1) enhancing the very small residual amounts of LPL activity that these patients may have, below the limit of detection of the assay in many cases (2) potentially enhanced activity of other lipases also involved in the metabolism and breakdown of TGs, such as hepatic lipase or endothelial lipase (Kinnunen and Ehnolm 1976), and (3) apoC-III interaction with Apolipoprotein E (apoE), an important factor in liver reuptake of lipid particles by blocking apoE-mediated uptake of lipid particles in the liver (Breyer et al. 1999), and therefore, reducing apoC-III might enhance apoE-mediated uptake of lipid particles. Volanesorsen-mediated reduction of apoC-III could be contributing to one or all of these mechanisms resulting in the observed potent and sustained reductions in TG.

Through a novel apoC-III lowering mechanism of action, volanesorsen may provide the potential to manage triglyceride levels in FCS patients.

2.3 Volanesorsen

2.3.1 Mechanism of Action

Volanesorsen is a second-generation antisense oligonucleotide (ASO) drug targeted to human apoC-III. It is complementary to a region within the 3′ untranslated region of the apoC-III messenger ribonucleic acid (mRNA) and binds to the mRNA by Watson and Crick base pairing.

The hybridization (binding) of volanesorsen to the cognate mRNA, results in the RNase H1-mediated degradation of the apoC-III mRNA, thus preventing production of the apoC-III protein. Maximal antisense-mediated reduction of target mRNA levels is typically greater than 90% of control levels in sensitive tissues (Crooke and Bennett 1996; Zhang et al. 2010). Furthermore, reduction in target mRNA levels using this approach correlates directly with a subsequent reduction in target protein levels.

2.3.2 Chemistry

Chemically, volanesorsen is a synthetic oligomer of 20 nucleotides (i.e., a 20-mer) that are connected sequentially by phosphorothioate linkages. The nucleotide sequence of volanesorsen (Figure 2) is complementary to a 20-nucleotide stretch within the 3′ untranslated region of the apoC-III mRNA transcript at base position 489-508. Structurally, the oligonucleotide has 3 regions. Two (2) of them, the 5 nucleotides at the 5′ end and the 5 nucleotides at the 3′ end, are composed of 2′-*O*-(2-methoxyethyl) (MOE)-modified ribonucleotides. These MOE-modified nucleotides confer (1) increased affinity to the target mRNA (Altmann et al. 1996; McKay et al. 1999), (2) increased resistance to exonucleases and endonucleases (thereby increasing stability in tissue) (Geary et al. 2003), and (3) amelioration of some of the high dose toxicities thereby resulting in an improved safety profile compared to first generation antisense drugs containing phosphorothioate modified oligodeoxynucleotides (DNA) (Henry et al. 2000). The third region, the central portion of the oligonucleotide, is composed of 10 oligodeoxynucleotides. This chimeric design is called a MOE-Gapmer, and volanesorsen employs this chimeric structure to enable use of the RNase H1-mechanism for antisense activity. This is because while the 2′-MOE modification confers increased stability and affinity, it does not support RNase H1 catalysis of RNA hybridized to 2′-MOE-modified nucleotides (McKay et al. 1999). This is caused by conformational changes induced in the heteroduplex by 2′-alkoxy:RNA hybrids that are not recognized by RNase H1 enzymes (Inoue et al. 1987; Monia et al. 1993). By limiting the 2′-MOE modification to nucleotides flanking the phosphorothioate oligodeoxynucleotide core, the beneficial attributes of the 2′-MOE chemistry are preserved while also retaining RNase H1 recognition.

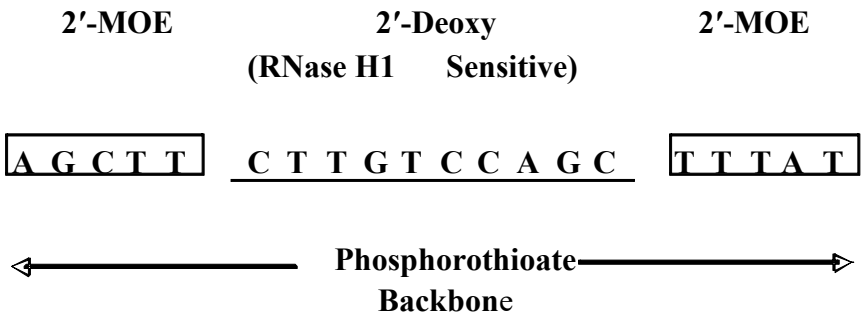


Figure 2 Design of Chimeric 2′-MOE Phosphorothioate Oligonucleotides (MOE-Gapmer). The sequence of volanesorsen is shown

2.3.3 Preclinical Experience

Inhibition of apoC-III using volanesorsen has been shown to potently reduce hepatic apoC-III mRNA as well as plasma apoC-III protein and TG in a dose- and time-dependent fashion in several species, including human apoC-III transgenic mice, and other rodent and monkey models. Treatment with volanesorsen also resulted in reduced VLDL and chylomicron TG and reduced postprandial TG in hypertriglyceridemic monkeys (Graham et al. 2013).

The pharmacokinetics (PK) and toxicity of volanesorsen have been assessed in mice, rats, and cynomolgus monkeys. General toxicity studies with volanesorsen for up to 39 weeks of treatment followed by up to a 20-week recovery period are complete. The preclinical toxicology program for volanesorsen consists of single dose safety pharmacology studies in the monkey (cardiovascular) and mouse (neurobehavioral and pulmonary assessment studies), *in vitro* and *in vivo* genetic toxicity assessment, repeat dose fertility and/or developmental reproductive toxicology studies in the mouse and rabbit and evaluation in the *in vitro* human Ether-á-go-go-related gene (hERG) assay.

Volanesorsen treatment-related findings in mice and monkeys were generally consistent with those expected for the 2′-MOE-class of ASOs. Treatment-related findings included effects consistent with drug accumulation in tissues in rodents and monkeys, species-dependent proinflammatory response in rodents and monkeys and complement activation and reductions in platelet counts in the monkey. In the mouse and monkey general toxicity studies, reduction of hepatic apoC-III mRNA (> 75%) was not associated with any findings that could be considered related to the pharmacologic inhibition of apoC-III for up to 39 weeks of treatment.

The long-term, chronic toxicology studies in rodents with volanesorsen produced a significant proinflammatory response that led to subsequent effects on the heart at high doses. The rodent species are most sensitive to the proinflammatory effects of antisense molecules. Importantly, these effects on the heart were not observed in the monkey chronic toxicity studies even at the highest doses tested where drug exposure was higher than that in rodents.

Because these changes were not observed in monkeys, the findings in the heart are considered to be rodent-specific and not relevant to humans. Nevertheless, such effects will be monitored by measurement of echocardiograms that will be included in this clinical study.

Volanesorsen caused no untoward effects in safety pharmacology studies (*in vitro* and *in vivo*) and was non-genotoxic (*in vitro* and *in vivo*). Volanesorsen had no effects on fertility or embryo/fetal development in the mouse or rabbit reproductive toxicity studies. In these studies, volanesorsen was detected in placental tissue but not in fetal tissue indicating that little, if any, drug was able to cross the placenta to reach the fetus. Reduction of apoC-III mRNA (64% in males and 47% in females) also did not affect fertility or cause untoward effects on embryo/fetal development in mice.

Detailed information concerning the preclinical studies conducted with volanesorsen can be found in the volanesorsen Investigator's Brochure.

2.3.4 Clinical Experience

Detailed information concerning the clinical studies conducted with volanesorsen can be found in the volanesorsen Investigator's Brochure. A summary is included below.

Volanesorsen has been evaluated in one Phase 1 study and two Phase 2 studies, all double blinded and placebo controlled. The total exposures comprise 99 patients and healthy volunteers administered volanesorsen from 50 to 400 mg subcutaneously up to 3 months (compared to 37 administered placebo).

All clinical trials of volanesorsen have shown large and clinically meaningful reductions in fasting plasma apoC-III and TG (~80% and 70%, respectively, mean reduction from baseline with 300 mg dose) with a very high degree of consistency of response between the different patient groups. This includes healthy volunteers, patients with moderate to severe hypertriglyceridemia not on background TG-lowering therapy, patients with moderate to severe hypertriglyceridemia on a background stable fibrate therapy (Gaudet et al. 2015), patients with FCS, and patients with T2DM.

In a Phase 2 study, 3 patients with FCS were treated with 300 mg/wk volanesorsen in an open-label fashion. These patients had a mean baseline fasting TG level of 1,844 mg/dL and all 3 patients achieved TG levels below or close to 500 mg/dL during the dosing period out to Day 92 (Figure 3). Two (2) of the FCS patients had an absolute reduction in fasting TG in excess of 1,500 mg/dL (Gaudet et al. 2014).

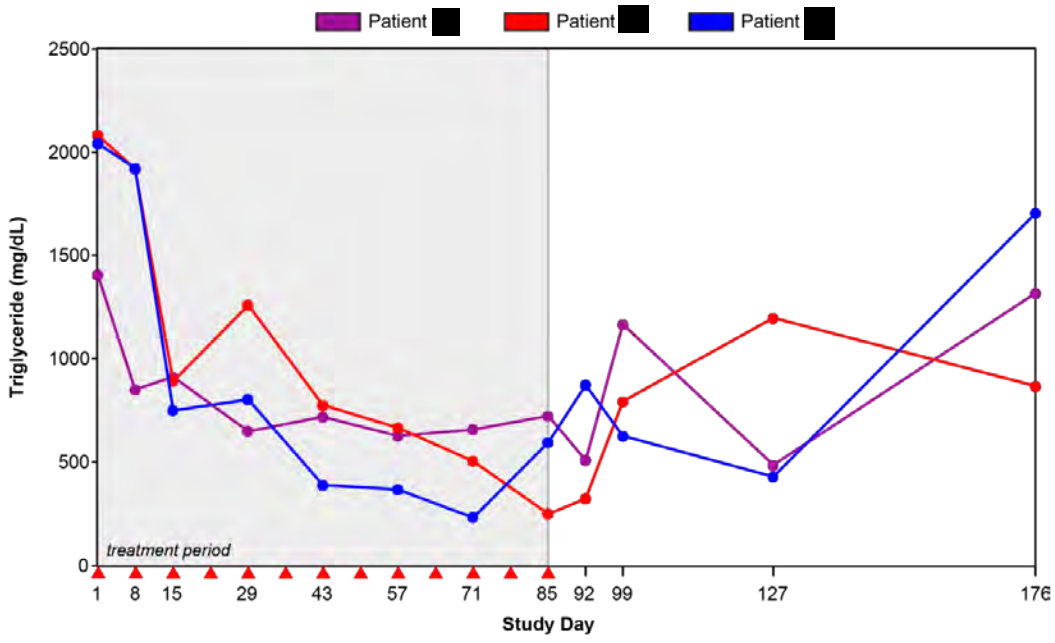


Figure 3 Fasting Triglycerides in Patients with FCS Treated with Volanesorsen

In clinical studies conducted to date volanesorsen has been well-tolerated and has shown a favorable safety profile. There has been no clinical or laboratory evidence of drug-drug interactions.

In the completed studies, there have been no volanesorsen associated laboratory abnormalities suggestive of an effect on the renal (serum creatinine, proteinuria) or hepatic systems (alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin). In Phase 2 studies, there was a mild decrease of platelet count associated with volanesorsen administration that recovered in the post-treatment period and was not associated with platelet-related adverse events (AEs). In the blinded ongoing clinical trials of ISIS 304801, 2 patients of 142 dosed (as of February 29, 2016) had a decrease in platelet count to less than 50,000/mm^3 in the absence of major bleeding or clinically-relevant non-major bleeding and had Study Drug paused as per the monitoring and stopping rules for platelet counts (Section 8.6.3). Platelet counts recovered following suspension of dosing.

The most frequently observed AEs with volanesorsen were local reactions at the injection site. Local cutaneous reactions at the injection site defined as those events presenting as either pain, tenderness, erythema, pruritus or swelling occurring on the day of injection and persisting for at least 2 days were infrequent (~15% of injections), were almost always mild, resolved spontaneously, were non-progressive, and were not associated with systemic sequelae.

2.4 Rationale for Dose and Schedule of Administration

The dose and schedule selected for this study is 300 mg per week for 52 weeks. The dose of 300 mg per week is supported by both the cumulative nonclinical data available to date and the Phase 2 clinical data. In nonclinical studies, volanesorsen treatment-related effects in rodents and monkeys were consistent with drug accumulation in tissues and also include species-specific proinflammatory responses. In the monkey, the No-Observed-Adverse-Effect Level (NOAEL) was defined by the cumulative clinical pathology results and histopathology data which provide an adequate clinical margin. No nonclinical findings were considered to be related to the pharmacologic inhibition of apoC-III.

The safety data to date suggest that volanesorsen has been well-tolerated at dose levels up to 300 mg in patients with high triglycerides (including type 2 diabetes patients and administration in combination with fibrates and statins) with the most common AEs being local to the injection site and predominantly mild. A pooled analysis of safety for the Phase 2 studies did not demonstrate any clear difference in safety or tolerability between the different doses tested (100 mg, 200 mg, and 300 mg per week for 13 weeks).

Analysis of the cohorts in which volanesorsen was studied at different doses demonstrates dose-dependent pharmacology with respect to pharmacodynamic (PD) effect on the target, apoC-III, with a clear difference in the TG-lowering effect between the different doses in the 100 mg to 300 mg dose range as compared to placebo.

In addition to the nonclinical and clinical experience of volanesorsen, the dose and schedule of administration is supported by the preclinical and clinical safety experience of several other 2′-MOE-modified ASOs that have been safely administered intravenously and subcutaneously in multiple clinical studies at doses up to 1000 mg and for treatment durations that exceed 24 months (Santos et al. 2015).

3. EXPERIMENTAL PLAN

3.1 Study Design

This is an open-label study of:

Group 1: ISIS 304801-CS6 (index study) roll-over FCS patients

Group 2: ISIS 304801-CS16 (index study) roll-over FCS patients

Up to approximately 70 patients will receive 300 mg once weekly volanesorsen for 52 weeks.

Following the Week 52 visit, patients will have the option of participating in an expanded access program or continuing dosing for up to an additional 52 weeks until an expanded access program is approved and available in their country. Patients not participating in an expanded access program will enter a 13-week post-treatment evaluation period.

3.2 Number of Study Centers

This study will be conducted at multiple centers worldwide.

3.3 Number of Patients

Up to approximately 70 patients will be dosed.

3.4 Overall Study Duration and Follow-up

The Study will consist of the following periods:

3.4.1 Qualification

A Qualification period of up to 2 weeks (unless approved by the Sponsor) is given to complete qualification assessments outlined in the Schedule of Procedures. Please refer to Section 4.1 and Appendix A.

3.4.2 Treatment

The treatment period is 52 weeks. Eligible patients will report to the Study Center for assessments at specified intervals throughout the 52-week treatment period as detailed in the Schedule of Procedures (Appendix A). During the treatment period, volanesorsen is administered by SC injection once weekly.

3.4.3 Post-Treatment

The post-treatment evaluation period is 13 weeks and consists of 7 Study Center visits on Weeks 53, 54, 55, 56, 57, 58, and 65 (Weeks 53, 54, 55, 56, 57, and 58 may be conducted by a home healthcare nurse).

3.5 End-of-Study

The End-of-Study is last patient, last visit.

3.6 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will review (as needed) safety, tolerability and efficacy data collected on volanesorsen during this study. Based on its ongoing assessment of the safety and tolerability of volanesorsen, the DSMB will provide recommendations to the Sponsor for modifying, stopping or continuing the study as planned. Details on the safety assessments, frequency of review and meeting schedules are outlined in the DSMB Charter and/or the statistical analysis plan (SAP).

4. PATIENT ENROLLMENT

4.1 Qualification

Before patients may be enrolled into the study, the Sponsor requires a copy of the Study Center's written independent ethics committee/institutional review board (IEC/IRB) approval of the protocol, informed consent form, and all other patient information.

Patients or their legally acceptable representatives must sign the consent form before any study-specific procedures or evaluations related to this open-label study are performed.

During the qualification period, the eligibility of the patient to enroll in the open-label study will be determined. Final assessments from the ISIS 304801-CS6 or ISIS 304801-CS16 studies may be used for qualification. A period of up to 2 weeks after completion of the ISIS 304801-CS6 or ISIS 304801-CS16 index studies (unless approved by the Sponsor) is given to complete qualification. Qualified patients will retain the unique patient identification number that was assigned to them during the ISIS 304801-CS6 or ISIS 304801-CS16 index studies. The patient identification number will be used to identify the patient throughout the extension trial and must be used on all study documentation related to that patient. The patient identification number must remain constant throughout the extension trial.

4.2 Enrollment

Patients will be enrolled into the treatment phase of the study after all qualification assessments have been completed and after the Investigator has verified that they are eligible per criteria in Sections 5.1 and 5.2. No patient may begin treatment prior to enrollment.

Eligible patients will be enrolled using an Interactive Voice/Web-Response System (IXRS).

5. PATIENT ELIGIBILITY

To be eligible to participate in this study candidates must meet the following eligibility criteria within 2 weeks of Study Day 1, or at the time point specified in the individual eligibility criterion listed.

5.1 Inclusion Criteria

1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law
2. Age ≥ 18 years at time of informed consent

3. Groups 1 and 2: Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement.

   Group 2: Patients who enrolled in ISIS 304801-CS16 must also meet the following criteria in order to enter into the open-label Study:

   a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L)

   b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) supported by documentation of at least 1 of the following:

      - Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1)
      - Post heparin plasma LPL activity of ≤20% of normal in medical history. Note: testing of LPL activity should not be performed to confirm eligibility for the study

   c. Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Qualification for the ISIS 304801-CS16 index study

4. Able and willing to participate in a 65-week study
5. Satisfy 1 of the following:

   a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved), abstinent*, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration.

   b. Males: Surgically sterile, abstinent* or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration.

*Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception

5.2 Exclusion Criteria for Group 1 (ISIS 304801-CS6) and Group 2 (ISIS 304801-CS16) Index Study Roll-over Patients

1. Have any new condition or worsening of existing condition which in the opinion of the Investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study.

2. Unwilling to comply with lifestyle requirements for the duration of the study (Section 6.3).

6. STUDY PROCEDURES

6.1 Study Schedule

All required study procedures are outlined in Appendices A, B, C, and D.

6.1.1 Qualification

Please refer to Section 4.1 and Appendix A.

6.1.2 Treatment Period

The patients, Investigators, study staff, and the Sponsor will remain blinded to lipid data through the last patient's Week 13 visit of the open-label study or until results from the database locks for the ISIS 304801-CS6 and ISIS 304801-CS16 index studies become available, whichever comes first.

During the treatment period, patients will report to the study center for clinic visits a minimum of 5 times during Weeks 1-52 (see Schedule of Procedures in Appendix A). Study Drug will be administered once weekly unless the patient is on a biweekly dosing schedule for safety reasons (Section 8.1). Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), AEs, concomitant medication/procedure information, lipid panel, blood viscosity, volanesorsen plasma concentrations, immunogenicity (IM) testing, platelet aggregation, liver/spleen MRI, ECGs, echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Adverse events at the injection site should be collected as adverse events. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period and all patients will complete a daily food diary for one week prior to their quarterly visit. All blood and urine samples should be collected prior to volanesorsen administration. Blood sampling at Weeks 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, and 51 may be conducted by a home healthcare nurse. Approval for study procedures to be conducted by a home healthcare nurse on other outpatient visit days will require prior approval by the Sponsor. Patients must be fasted prior to drawing all blood samples and samples drawn locally should also be sent to the central laboratory for analysis whenever possible. Dosing instructions and training will be provided to the patient where applicable.

All reasonable attempts should be made to ensure compliance with the visit schedule as outlined in Appendix A. However, in the event that a visit does not occur or is delayed, all subsequent visits should be calculated based on the time elapsed since Day 1 rather than from the date of the previous visit.

6.1.3 Extended Treatment Period

Patients will have the option of continuing dosing for up to an additional 52 weeks until an expanded access program is approved and available in their country.

During the extended treatment period, patients will report to the study center for clinic visits during Weeks 54-104 (see Schedule of Procedures in Appendix A). Study Drug will be administered once weekly unless the patient is on a biweekly dosing schedule for safety reasons (Section 8.1). Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), AEs, concomitant medication/procedure information, lipid panel, volanesorsen plasma concentrations, IM testing, ECGs, and physical examinations will be performed according to the Schedule of Procedures in Appendix A. Adverse events at the injection site should be collected as adverse events. Dietary counseling will be reinforced at intervals throughout the extended treatment period. All blood and urine samples should be collected prior to volanesorsen administration. Blood sampling at Weeks 53, 54, 55, 56, 57, 58, 59, 60, 61, 62,63, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, and 103 may be conducted by a home healthcare nurse. Approval for study procedures to be conducted by a home healthcare nurse on other outpatient visit days will require prior approval by the Sponsor. Patients must be fasted prior to drawing all blood samples and samples drawn locally should also be sent to the central laboratory for analysis whenever possible. Dosing instructions and training will be provided to the patient where applicable.

6.1.4 Pharmacokinetic (PK) Subgroup

A subgroup of patients will participate in an extended PK collection. Patients in this subgroup will have more frequent PK sampling over a 24-hour period following the first dose on Study Day 1 in order to evaluate the plasma PK parameters of volanesorsen. Patients in this subgroup will have an additional visit to the clinic, or by a home healthcare nurse, on Day 2 to collect a 24-hour post-dose blood draw after dosing on Day 1. The detailed PK sampling schedules are outlined in Appendix C.

Participation in the PK subgroup is optional for sites and patients, and consent may be withdrawn for the subgroup-specific procedures (e.g., multiple blood draws for PK) without being withdrawn from the study. If a patient withdraws consent from the subgroup procedures, he/she should remain on study and continue to follow all the non-subgroup assessments and procedures as outlined in Appendix A.

6.1.5 Post-Treatment Period

After completion of the Week 52 visit assessments, patients will have the option of participating in an expanded access program or continuing dosing for up to an additional 52 weeks until an expanded access program is approved and available in their country as described in Section 6.1.3. Patients not participating in an expanded access program will enter the 13-week post-treatment evaluation period. This 13-week post-treatment evaluation period consists of 7 Study Center visits on Weeks 53, 54, 55, 56, 57, and 58 (which may be conducted by a home healthcare nurse), and Week 65 as outlined in the Schedule of Procedures in Appendix A. Patients who complete, or terminate early from, the extended treatment period without subsequently participating in an expanded access program will enter a 13-week post-treatment evaluation period consisting of 7 Study Center visits on Weeks 105, 106, 107, 108, 109, and 110 (which may be conducted by a home healthcare nurse), and Week 117 as outlined in the Schedule of Procedures in Appendix A.

6.2 Additional Study Assessments

6.2.1 Laboratory Assessments

Laboratory analyte samples will be collected throughout the study. A list of these analytes is contained in Appendix B.

Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1-week and the result must be reviewed by the Investigator and confirmed to be acceptable before dosing can continue. All platelet count results will be promptly reviewed by the Investigator to determine if the count has met a stopping rule, or the dose reduction rule of 100,000/mm^3, or the dose pause rule of 75,000/mm^3.

Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor.

6.2.2 Physical Exams and Vital Signs

Physical exams and vital signs will be performed as indicated in the Schedule of Procedures (Appendix A). Vital signs should include weight, blood pressure, pulse rate, respiratory rate and body temperature. Blood pressure and pulse rate will be recorded after the patient has been in a sitting position for at least 5 minutes. Semi-supine systolic and diastolic blood pressure should always be measured on the same arm (preferentially on the left arm). Height will be measured at the Day 1 visit.

6.2.2.1 Eruptive Xanthoma

At each visit, patients will be asked whether they have had any episodes of eruptive xanthoma since their last visit and the number/duration of the events will be recorded. Physical exams should also include skin examination for presence/resolution of eruptive xanthomas. If a patient experiences an episode of eruptive xanthoma during the study, photos of the area should be taken, if possible.

6.2.2.2 Lipemia Retinalis

If possible, lipemia retinalis will be assessed by fundus photography prior to administration of the first dose of Study Drug (for ISIS 304801-CS16 roll-over patients) and repeated at Week 52. Images will be evaluated by an independent assessor, blinded to the patient's treatment assignment.

6.2.3 Echocardiography

Echocardiography for assessment of left and right ventricular function and mitral and aortic valve function will be conducted at Week 26 and Week 52 in all patients. For the purpose of assessment of treatment-emergent changes, all echocardiograms will be evaluated on an ongoing basis by an independent central reader. Results will be provided to the DSMB for their review.

6.2.4 ECG

The ECG will be recorded after the patient has been resting in a supine position for at least 5 minutes. ECGs will be performed in triplicate at Week 13, Week 26, Week 38, Week 52, and Week 65. Patients in the Extended Treatment Period will have ECGs performed in triplicate at Week 76 and Week 104.

6.2.5 MRI

MRI of the liver and spleen will be conducted at Week 52 for all patients for whom MRI is not contraindicated, e.g., patients having metal implants.

MRIs will be conducted using standardized procedures and settings. MRIs will be read by an independent central reader to assess liver fat and liver and spleen size**.**

6.2.6 Quality of Life Assessments

All patients will complete Quality of Life Questionnaires (EQ-5D and SF-36) at Week 1, Week 13, Week 26, Week 52, and Week 65.

6.2.7 Disease Symptom Diary

All patients will complete a symptom questionnaire once a week starting at the beginning of the qualification period and continuing to the end of the post-treatment follow-up period (Week 65).

6.2.8 Diet Monitoring

The diets of patients enrolled in the study will be monitored as follows:

1. All patients will be required to maintain a 7-day food diary prior to Week 1, Week 13, Week 26, Week 52, and Week 65.
2. Patients will receive diet/alcohol counseling by qualified study personnel at clinic visits throughout the course of the study. Qualified study personnel will telephone the patient to provide diet/alcohol counseling for visits that are conducted by a clinical service. Patients in the Extended Treatment Period will receive diet/alcohol counseling by qualified study personnel at clinic visits only.
3. In addition to the 7-day food diary and the diet /alcohol counseling during clinic visits, telephone calls from a dietitian or qualified study personnel to assess as to how each patient is maintaining their diet may be conducted randomly during the treatment and post treatment follow-up periods.

6.2.9 Family History

Family history of hypertriglyceridemia and pancreatitis will be collected for each patient.

6.2.10 Chart Review for Incidents of Acute Pancreatitis in Medical History (Group 2)

Patient records will be reviewed for incidents of acute pancreatitis occurring up to 5 years prior to Qualification and information relating to these events will be collected for independent adjudication.

6.3 Restriction on the Lifestyle of Patients

6.3.1 Contraception Requirements

All male patients and women of childbearing potential must refrain from sperm/egg donation and either be abstinent† or, if engaged in sexual relations of child-bearing potential, practice effective contraception from the time of signing the informed consent form until at least 13 weeks after their last dose of study treatment.

Male patients must also encourage their female partner to use effective contraception from the time of signing the informed consent until 13 weeks after the subject's last dose of study treatment.

For the purposes of this Study, women of childbearing potential are defined as any female who has experienced menarche, and who does not meet 1 of the following conditions:

- Postmenopausal: 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved
- 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Post hysterectomy

For the purposes of the study, effective contraception is defined as follows:

For male patients:

- Effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the use of condoms together with spermicidal foam/gel/film/ cream/suppository. Male patients must also encourage their female partner to use effective contraception from the time of signing the informed consent until 3 months after the patient's last dose of study treatment. Effective contraceptive for the female partner includes: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or barrier methods (female condom*, diaphragm, sponge, cervical cap) together with spermicidal foam/gel/film/cream/suppository. Male patients with partners that are pregnant must use condoms to ensure that the fetus is not exposed to the Study Drug.

For female patients:

- Using 1 or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or any 2 barrier methods (a combination of male or female condom* with diaphragm, sponge, or cervical cap) together with spermicidal foam/gel/film/cream/suppository.

* Note: A female condom and a male condom should not be used together as friction between the two can result in either product failing.

† Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception

6.3.2 Other Requirements

All patients will be required to fast for at least 10 hours and preferably not more than 12 hours before visits requiring fasted blood sampling.

All patients will be encouraged to follow a diet comprising ≤ 20 g fat per day during the study.

Alcohol should not be consumed during the study.

All patients will be given an instruction card that must be presented to the treating physician if a suspected case of pancreatitis occurs. The card will explain that the patient is in a clinical trial and that serum lipase and/or amylase measures should be done in order to adjudicate the event, based on Atlanta Classification (Banks et al. 2013). If serum or amylase activity is less than 3 x upper limit of normal (ULN), imaging, preferably contrast-enhanced computed tomography, should be considered to confirm the diagnosis of acute pancreatitis per the Atlanta Criteria.

7. STUDY DRUG

7.1 Volanesorsen Description

Volanesorsen drug product (ISIS 304801) characteristics are listed in Table 1.

Volanesorsen (ISIS 304801) is contained in glass prefilled syringes (PFS). Volanesorsen and its storage and preparation instructions will be provided by the Sponsor or designee. Volanesorsen must be stored securely at 2 to 8 °C and be protected from light.

Table 1 Volanesorsen (ISIS 304801) Characteristics

Strength	200 mg/mL
Volume/Formulation	1.5 mL solution per PFS
Dose	300 mg once weekly
Route of Administration	SC

7.2 Packaging and Labeling

The Sponsor will provide the Investigator with packaged volanesorsen labeled (ISIS 304801) in accordance with specific country regulatory requirements.

7.3 Study Drug Accountability

The study staff is required to document the receipt, dispensing, and return/destruction of volanesorsen provided by the Sponsor. The Study Center must return all unused volanesorsen to the Sponsor or designee. All used syringes must be disposed of as per the site's hazardous waste destruction policy.

8. TREATMENT OF PATIENTS

8.1 Volanesorsen Administration

For each individual patient, volanesorsen will be administered subcutaneously as a single 1.5 mL 300 mg injection once weekly for Weeks 1-52. Patients entering this ISIS 304801-CS7 study on a reduced dose or dose frequency of Study Drug (volanesorsen), for safety or tolerability reasons in their index study (ISIS 304801-CS6 or ISIS 304801-CS16), will receive a reduced dose or dose frequency of volanesorsen for continued safety or tolerability as outlined in Sections 8.5 and 8.6. Patients entering this CS7 study having dose or dose frequency reduced in the CS16 index study after 13 weeks of treatment, as outlined in CS16 Amendment 4 Section 8.7, can receive the 300 mg once weekly dose of volanesorsen.

Patients should receive 1 dose per week, with weeks always defined relative to Study Day 1. For example, if a patient receives the first dose on a Monday, subsequent doses should be given on Mondays, if possible. If a patient misses an injection, or if dosing on the usual day is not possible, the patient can reschedule the injection provided that 2 doses are administered at least 2 days apart.

Please refer to the Study Drug Manual provided by the Sponsor for more detailed instructions for volanesorsen preparation and administration.

8.2 Other Protocol-Required Drugs

There are no other protocol-required drugs.

8.3 Other Protocol-Required Treatment Procedures

There are no other protocol required treatment procedures for this study.

8.4 Treatment Precautions

There are no specific treatment precautions required for this study.

8.5 Safety Monitoring Rules

Please refer also to the 'Guidance for Investigator' section of the Investigator's Brochure.

For the purposes of safety monitoring baseline is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 (e.g., qualification assessments or assessments from the final visits of ISIS 304801-CS6 and ISIS 304801-CS16 index studies if used for qualification).

In addition to the standard monitoring of clinical safety parameters, the following guidelines are provided for the monitoring of selected parameters chosen based on preclinical and clinical observations.

Confirmation Guidance: At any time during the study (Treatment or Post-Treatment Periods), the initial clinical laboratory results meeting the safety monitoring or stopping criteria presented below **must be confirmed** by performing measurements (ideally in the same laboratory that performed the initial measurement) on new specimens. All new specimen collections should take place as soon as possible (ideally within 3 days of the initial collection). For stopping rules,

if the initial laboratory result is observed during the Treatment Period, the results from the retest **must be available** prior to administering the next dose of volanesorsen.

In addition to the safety monitoring parameters listed below, the Sponsor may request confirmation of additional lab values.

Re-dosing Guidance: Patients with initial laboratory test values that reach a stopping rule must not be re-dosed until the re-test results are available. In general, patients who do not meet the stopping rules based upon retest may continue dosing. However, the Investigator and the Sponsor Medical Monitor (or appropriately qualified designee) should confer as to whether additional close monitoring of the patient is appropriate. Reduction in dose or dose frequency may also be initiated as noted in Section 8.7. If any of the stopping criteria described below (refer to Sections 8.6.1 to 8.6.3) are met, the patient will be dose paused or permanently discontinued (as described in the stopping criterion concerned) from further treatment with volanesorsen, and evaluated fully as outlined below and in consultation with the Sponsor Medical Monitor or appropriately qualified designee, and will be followed up in accordance with Section 8.8 of the protocol.

8.5.1 Safety Monitoring for Liver Chemistry Tests

The following rules are adapted from the draft guidance for industry, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," issued by the U.S. Department of Health and Human Services, Food and Drug Administration, July 2009. For a definition of Baseline please refer to guidance in Section 8.5 above.

In the event of an ALT or AST measurement that is > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) at any time during the study (Treatment or Post-Treatment Period), the initial measurement(s) should be confirmed as described above. Additional confirmatory measurements should also be performed if ALT or AST levels increase to 5 x ULN.

Frequency of Repeat Measurements: Patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) should have their liver chemistry tests (ALT, AST, alkaline phosphatase (ALP), international normalized ratio (INR) and total bilirubin) retested at least once-weekly until ALT and AST levels become ≤ 1.2 x ULN or 1.2 x baseline value if the baseline value was > ULN.

Further Investigation into Liver Chemistry Elevations: For patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), the following evaluations should be performed:

1. Obtain a more detailed history of symptoms and prior and concurrent diseases
2. Obtain further history for concomitant drug use (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
3. Obtain a history for exposure to environmental chemical agents and travel

4. Serology for viral hepatitis (HAV IgM, HBsAg, HCV antibody, CMV IgM, and EBV antibody panel)
5. Serology for autoimmune hepatitis (e.g., antinuclear antibody [ANA])

Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic CT or MRI scans, may be performed at the discretion of the Investigator, in consultation with the Sponsor Medical Monitor. Repetition of the above evaluations should be considered if a patient's ALT and/or AST levels reach 5 x ULN.

8.5.2 Safety Monitoring for Platelet Count Results

Actions to be taken in the event of reduced platelet count are shown in Table 3 in Section 8.6.3.

Monitor every 1 week unless otherwise specified.

Study Drug administration is contingent on the availability of the immediately preceding test result. An interpretable platelet value must be available within 7 days prior to dosing. Only the study doctor or qualified designee can authorize continued Study Drug administration based on an acceptable platelet value. Patients should not administer a dose until they have been contacted by their study doctor or designee and told that it is acceptable to dose. Authorization to dose must be documented in the patient's medical records.

Due to the 1 to 2-year study duration it is anticipated that patients may undertake travel including vacations, which may impede weekly platelet monitoring. In some situations, it may be possible to arrange for local laboratory testing or use of the home healthcare service at their temporary location. The intent is to maintain weekly platelet monitoring and dosing where possible, as well as Investigator site contact with the study patients. However, if the above options are not possible, a temporary interruption of study treatment will be planned with a prompt blood draw upon the patient's return which must be reported and reviewed by the Investigator prior to the patient resuming dosing.

The tests outlined in Table 2 should also be performed as soon as possible. Additional lab tests will be determined by the Sponsor Medical Monitor or designee in consultation with the Investigator.

Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor (See also Stopping Rules Section 8.6.3).

Table 2 Labs to Be Performed in the Event of a Platelet Count Less than the Lower Limit of Normal (x2) or < 100,000/mm^3 (x1)*

*In patients who have any 2 occurrences (consecutive or non-consecutive) of platelet count less than the lower limit of normal or who have any 1 occurrence of platelets < 100,000/mm^3. Labs only need to be performed once. Labs may be collected over multiple visits, if blood requirements are a concern, as per investigator discretion.

Note: The following labs may change as additional data is assessed, and sites will be updated regarding any changes.

To Be Performed at Local Lab
Peripheral smear (should be performed locally, fixed and sent to central lab for review)
Fibrinogen split products or D-dimer on fresh blood
To Be Performed at Central Lab
Citrated sample for platelets
Coagulation panel (PT/INR, aPTT)
CBC with reticulocytes
Folate (folic acid)
Vitamin B12
Fibrinogen
von Willebrand factor
Total globulins, total IgA, IgG and IgM
Complement: total C3, total C4, Bb, C5a
hsCRP
Helicobacter pylori (breath test)
Serology for:
HBV, HCV, HIV (if not done recently for Qualification)
Rubella
CMV
EBV
Parvo B19
Auto-antibody screen:
Antiphospholipid
Rheumatoid factor
Anti-dsDNA
Anti-thyroid
To Be Performed at Specialty Lab(s)
Antiplatelet antibodies and Anti-PF4 assay
Anti-ASO antibody

8.5.3 Safety Monitoring for Minor Bleeding Events

Minor bleeding events are those that do not fulfill the criteria for major bleeding or clinically-relevant, non-major bleeding events (which are defined in Section 8.6.3), for example excess bruising, petechiae, gingival bleeding on brushing teeth. If a minor bleeding event occurs, the Investigator must notify the Sponsor Medical Monitor and additional testing of coagulation parameters activated partial thromboplastin time (aPTT), prothrombin time (PT), INR and platelet count should be performed.

8.5.4 Safety Monitoring for Constitutional Symptoms

Patients will be instructed to promptly report any signs of symptoms of fever or constitutional symptoms that may arise during the study and the Investigator should closely evaluate all potential causes, including concomitant illness. Patients that experience persistent constitutional symptoms should be discussed with the Sponsor Medical Monitor or designee to determine whether additional monitoring or laboratory tests are required.

8.5.5 Safety Monitoring for LDL-C Elevations

Beginning at Week 13, laboratory alerts will be in place to notify the Investigator if a patient has a low-density lipoprotein-cholesterol (LDL-C) > 160 mg/dL (> 130 mg/dL for patients with T2DM) on 2 consecutive visits. If this occurs, LDL-C values for this patient will be unblinded for the remainder of the study and the Investigator will be encouraged to initiate/adjust treatment to lower LDL-C according to country-specific guidelines (e.g., initiate statin therapy or increase the statin dose for patients who are already on treatment).

8.5.6 Safety Monitoring for Insulin, Oral Antidiabetic Medication and Glucose

All patients on insulin will monitor their glucose levels with a glucometer as per standard practice guidelines and bring their glucometer or glucometer log printout to every clinic visit. In addition, patients who are not on insulin but use a glucometer should also bring their glucometer and/or glucometer log printout to every clinic visit.

- The Investigator or delegate will review the glucometer reading or printout at every clinic visit to evaluate if fasting pre-breakfast self-monitored plasma glucose values exceed threshold values as per the Safety Monitoring Rules for Hyperglycemia below.

All diabetic patients will note any changes in their insulin dose and /or oral antidiabetic therapy, as well as any hypoglycemic episode they may experience.

- The Investigator or delegate will ask patients at every clinic visit if they made changes in their insulin dose or oral antidiabetic therapy, and if they experienced a hypoglycemic episode.
    - Patients will be instructed on the monitoring and management of hypoglycemic episodes at each visit.
    - Documented symptomatic hypoglycemic episodes should be captured as adverse events in the adverse event CRF. Documented symptomatic hypoglycemia is defined as typical hypoglycemia symptoms accompanied by measured plasma glucose ≤ 70 mg/dL (≤ 3.9 mmol/L).

- Any changes in insulin dose or oral antidiabetic therapy should be captured into the Concomitant Medication CRF.

8.5.7 Safety Monitoring for Documented Severe Hypoglycemia

A **documented severe hypoglycemic event** is defined as 1 in which the patient requires assistance of another person to obtain treatment for the event and has a plasma glucose level ≤ 70 mg/dL (≤ 3.9 mmol/L). The rescue treatment of hypoglycemia may include IV glucose or buccal or intramuscular glucagon.

The definition of severe symptomatic hypoglycemia includes all episodes in which neurological impairment was severe enough to prevent self-treatment and which were thus thought to place patients at risk for injury to themselves or others. Note that "requires assistance" means that the patient could not help himself or herself. Someone being kind that assists spontaneously the patient when not necessary does not qualify as "requires assistance."

Severe hypoglycemia will be qualified as a SAE only if it fulfills SAE criteria.

If a patient presents with symptoms of hypoglycemia, the Investigator will need to take immediate action to confirm the patient's glucose level and treat the patient accordingly.

The experience of hypoglycemia may vary greatly from patient to patient. However, there are certain classical signs and symptoms, of which patients should be aware as a clue that their blood glucose may be low. Common symptoms include headache, heart pounding, confusion, disorientation, numbness or tingling, pale skin, shakiness or tremulousness, increased appetite, anxiousness or nervousness, lightheadedness or dizziness, sweating, and weakness. Coma could occur if blood sugar correction is not performed.

If patients suspect they might be having a hypoglycemia reaction, they should check their blood glucose using their meters as soon as possible, before treatment if possible, provided they feel it is safe to do so. If there is doubt about safety they should treat the event first, using some sugar, milk, or juice for example, then obtain and record a blood glucose value as soon as possible thereafter. The time and nature of treatment should be noted, and especially if any blood glucose result was before or after treatment. It would be helpful for the patient to note if a contributory factor (e.g., missed or reduced meals, unaccustomed physical activity) occurred earlier in the day of the event.

8.5.8 Safety Monitoring for Hyperglycemia

Upward dose titration and/or addition of any other anti-hyperglycemic agent(s) will not be allowed during the course of the study, unless specific threshold values are met at Week 13 or later and confirmed on subsequent testing (ideally within 1-week of the initial test).

HbA1c is monitored every 3 months throughout the study. In addition, patients on insulin should self-monitor their plasma glucose (SMPG) routinely on a glucometer as per practice guidelines. If a fasting pre-breakfast SMPG value exceeds the specific glycemic limit, the patient should check it again on the following 2 days. If all the fasting pre-breakfast values on 3 consecutive days exceed the specific limit, the patient should contact the Investigator and an unscheduled central laboratory FPG measurement and HbA1c should be performed.

The threshold values are defined as:

- FPG > 270 mg/dL (15.0 mmol/L)
- HbA1c > 9% (for patients with baseline HbA1c < 8% and HbA1c increase of more than 1% from baseline (for patients with baseline HbA1c ≥ 8 and < 9%)

In case of confirmed FPG/HbA1c above the threshold value, the Investigator should ensure that no reasonable explanation exists for insufficient glucose control and in particular that:

- Plasma glucose was actually measured in the fasting condition (i.e., after at least 10 hours fast)
- Absence of intercurrent disease which may jeopardize glycemic control. In case of an emergency (e.g., surgery, infection), the Investigator can take appropriate measures for glycemic control
- Compliance to treatment is appropriate
- Compliance to diet and lifestyle is appropriate

If any of the above can reasonably explain the insufficient glycemic control, the Investigator should consider the following:

- Investigation and treatment of intercurrent disease (to be reported in adverse event (AE)/concomitant medication parts of the e-CRF)
- Stress on the absolute need to be compliant to treatment
- Organize a specific interview with a Registered Dietician or other qualified nutrition professional and stress on the absolute need to be compliant to diet and lifestyle recommendations

A FPG/HbA1c follow-up assessment should be arranged after appropriate action has been taken. If none from the above-mentioned reasons can be found, or if appropriate action fails to decrease FPG/HbA1c under the threshold values, additional medication may be introduced at the Investigator's discretion and according to local guidelines after discussion with the Sponsor Medical Monitor.

8.5.9 Acute Pancreatitis

If a patient has an episode of acute pancreatitis, dosing with Study Drug should be suspended temporarily until the patient is clinically stable. The suitability of the patient for continued dosing and the need for any modification to treatment schedule (refer to Section 8.7) will be determined by the Investigator in consultation with the Study Medical Monitor.

8.6 Stopping Rules

For the purposes of stopping rules baseline is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1.

8.6.1 Stopping Rules for Liver Chemistry Elevations

In the event of laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor,** dosing of a patient with volanesorsen will be stopped permanently; values that are not confirmed due to failure to retest or missing lab values will be presumed confirmed:

1. ALT or AST > 8 x ULN, which is confirmed
2. ALT or AST > 5 x ULN, which is confirmed and persists for ≥ 2 weeks
3. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed **and** total bilirubin > 2 x ULN or INR > 1.5
4. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed, and the new appearance (i.e., onset coincides with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> ULN) felt by the Investigator to be potentially related to hepatic inflammation

8.6.2 Stopping Rules for Renal Function Test Results

In the event of a persistent elevation that is observed over 2 consecutive weeks, for any of the 3 criteria below, dosing of a patient with volanesorsen may be stopped temporarily:

1. Serum creatinine increase that fulfill all of the following criteria: ≥ 0.3 mg/dL (26.5 µmol/L) and ≥ 40% above baseline creatinine values and > ULN
2. Proteinuria, dipstick 2 + (confirmed by dipstick retest and then further confirmed by a quantitative total urine protein measurement of > 1.0 g/24-hour)
3. Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault ≤ 40 mL/min that is confirmed by a 24-hour urine collection

The possible dosing re-initiation or follow-up schedule for any events meeting either of these criteria will be determined by the Investigator **in consultation with** the Sponsor Medical Monitor or designee.

8.6.3 Stopping Rules for Platelet Count Results

Actions to be taken in the event of a low platelet count are summarized in Table 3 below.

In the event of a platelet count less than 75,000/mm^3 that is associated with major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with volanesorsen will be stopped permanently. The follow-up schedule for any events meeting this stopping criterion will be determined by the Investigator in consultation with the Sponsor Medical Monitor.

In the event of any platelet count less than 50,000/mm^3, or a platelet count less than 75,000/mm^3 that occurs while the patient is on dosing at 300 mg every 2 weeks then dosing of a patient with volanesorsen will be stopped permanently. Platelet count will be monitored as outlined in Table 3.

Administration of steroids is recommended for patients whose platelet count is less than 50,000/mm^3. Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (**note:** may require continuation with oral steroids after methylprednisolone). Triglyceride levels be monitored weekly, and AE monitoring will continue, during corticosteroid treatment and the laboratory alert will be changed from an increase of 2,000 to 500 mg/dL during that period.

In the event of a platelet count less than 75,000/mm^3, and in the absence of major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with volanesorsen should be suspended temporarily until the platelet count has recovered to> 100,000/mm^3. If dosing is continued it should be at a reduced dose frequency of 300 mg every 2 weeks (refer to Section 8.7). The suitability of the patient for continued dosing will be determined by the Investigator in consultation with the Study Medical Monitor and will be based on factors such as the original rate of decline in the patient's platelet count, whether any bleeding events were experienced by the patient, and the speed of recovery of platelet count upon holding of dosing.

If after the first dosing rechallenge the platelet count again falls below 75,000/mm^3, then dosing of the patient with Study Drug will be stopped permanently.

Definition of Major Bleeding Events (Schulman et al. 2005):

- Fatal bleeding, and/or
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarterial or pericardial, or intramuscular with compartment syndrome, and/or
- Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more within 24 hours, or leading to transfusion of 2 or more units of whole or red cells

Definition of Clinically-Relevant, Non-Major Bleeding Events (Schulman et al. 2005):

1. Multiple-source bleeding
2. Spontaneous hematoma > 25 cm^2
3. Excessive wound hematoma (not injection site related)
4. Macroscopic hematuria (spontaneous or lasting > 24 hours if associated with an intervention)
5. Spontaneous rectal bleeding; epitasis, gingival bleeding, hemoptysis, hematemesis
6. Bleeding after venipuncture for > 5 minutes

Table 3 Actions in Patients with Low Platelet Count or Drop in Platelet Count

Platelet Count on Rx	Drug Dose	Monitoring
	Study Drug administration is contingent on the availability of the immediately preceding test result. An interpretable platelet value must be available within 7 days prior to dosing. Only the study doctor or qualified designee can authorize continued Study Drug administration based on an acceptable platelet value. Patients should not administer a dose until they have been contacted by their study doctor or designee and told that it is acceptable to dose. Authorization to dose must be documented in the patient's medical records.	**Monitor every 1 week unless otherwise specified** Obtain additional lab tests (Table 2) if 2 occurrences consecutive or non-consecutive) of platelet count 140K - > 100K/mm^3 or 1 occurrence of platelet count ≤ 100K/mm^3. Labs only need to be performed once. Labs may be collected over multiple visits, if blood requirements are a concern, as per investigator discretion.
> 100K/mm^3	Weekly 300 mg Study Drug administration	
100K/mm^3 - > 75K/mm^3	Permanently reduce dose frequency to 300 mg every 2 weeks	
75K/mm^3 - > 50K/mm^3	• If occurs while on dose of 300 mg every 2 weeks then permanently discontinue Study Drug, otherwise dose pause • When platelet count returns to > 100K/mm^3 restart dosing at dose frequency of 300 mg every 2 weeks **only if approved by Sponsor Medical Monitor**	• Monitor every 2-3 days until 2 successive values are > 75K/mm^3 then monitor every 1 week • Consider discontinuation of antiplatelet agents/NSAIDS/ anticoagulant medication
≤ 50K/mm^3	Permanently discontinue Study Drug	• Monitor daily until 2 successive values show improvement then monitor every 2-3 days until 2 successive values are >75K/mm^3 then monitor every 1 week • Patient should be evaluated by a hematologist to provide diagnostic and therapeutic management • Steroids recommended*. It is strongly recommended that, unless the patient has a medical contraindication to receiving glucocorticoids, the patient receives glucocorticoid therapy to reverse the platelet decline • Monitor triglyceride levels weekly and continue AE monitoring during steroid therapy • Discontinue antiplatelet agents/ NSAIDS/ anticoagulant medication while platelet count is< 50K/mm^3 if possible

* Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or methylprednisolone 30 mg/kg/day for 7 days (**note:** may require continuation with oral steroids after methylprednisolone)

8.7 Adjustment of Dose Frequency

Dose adjustments for platelet count reduction must be made in accordance with Section 8.6.3 and Table 3 (above).

Other dose adjustments, including dose interruptions, and/or decreasing the dose or dose frequency will be allowed for safety and tolerability. Any proposed adjustment to treatment schedule must be discussed with, and approved by, the Study Medical Monitor prior to initiation. Up to 2 adjustments in the treatment schedule may be allowed.

Patients may be dose paused in response to AEs after consultation with Study Medical Monitor.

8.8 Discontinuation of Study Treatment

A patient must permanently discontinue study treatment for any of the following:

- The patient becomes pregnant. Report the pregnancy according to instructions in Section 9.5.4
- The patient withdraws consent
- The patient experiences an AE that necessitates permanent discontinuation of study treatment
- The patient develops laboratory test abnormalities that meet any of the stopping rules listed in Section 8.6

The reason for discontinuation of study treatment must be recorded in the CRF and source documentation.

8.8.1 Follow-up Visits for Early Termination from Treatment Period

Any patient who discontinues early from the Treatment Period should be followed as per the platelet monitoring rules shown in in Section 8.6.3 for the first 6 weeks after discontinuing Study Drug. Following this period, if the platelet count is stable (at least 3 consecutive values that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3), the next platelet count should be taken within at least 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug. Patients should also be strongly encouraged to attend applicable landmark visits at Weeks 12, 13, 25, 26, and 50, 52 (calculated based on the time elapsed since Day 1) to collect fasting lipid panels and conduct safety assessments in accordance with the Schedule of Procedures in Appendix A. Any patient who discontinues treatment after Week 44 should also be strongly encouraged to attend a final follow-up visit (Week 65 visit assessments) approximately 13 weeks after their last dose of Study Drug, in addition to the applicable landmark visits.

If the patient declines or is unable to participate in the above, an early termination (ET) visit (Week 52 visit assessments) should be performed at the time of withdrawal, at a minimum, and ideally within 2 weeks from the last dose of Study Drug.

8.8.2 Follow-up Visits for Early Termination from Post-Treatment Follow-up Period

The patient who requests to withdraw from the study during the Post-Treatment Follow-up Period should be encouraged to follow the platelet monitoring rules shown in Table 3 in Section 8.6.3 for the first 6 weeks after discontinuing Study Drug. Following this period, if the platelet count is stable (at least 3 consecutive values that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3), the next platelet count should be taken within at least 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug. Patients should also be encouraged to undergo a final follow-up visit (Week 65 (or Week 117 if terminating from the Extended Treatment Follow-Up Period), see Appendix A) prior to leaving the study.

If a patient withdraws due to an AE at any time during the study, the Investigator should arrange for the patient to have appropriate follow-up until the AE has resolved or stabilized.

8.9 Withdrawal of Patients from the Study

Patients must be withdrawn from the study for any of the following:

- Withdrawal of consent
- The patient is unwilling or unable to comply with the protocol

Other reasons for withdrawal of patients from the study might include:

- At the discretion of the Investigator for medical reasons
- At the discretion of the Investigator or Sponsor for noncompliance
- Significant protocol deviation

All efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information, including the reason for withdrawal from study, must be recorded in the CRF.

Any patient who withdraws consent to participate in the study will be removed from further treatment and study observation immediately upon the date of request. These patients should be encouraged to complete the ET study procedures and observations at the time of withdrawal (see Section 8.8 and Appendix A).

For patients withdrawn for reasons other than withdrawal of consent every effort should be made to complete the early termination study procedures and observations at the time of withdrawal (see Section 8.8 and Appendix A).

8.10 Concomitant Therapy and Procedures

The use of concomitant therapies or procedures defined below must be recorded on the patient's CRF. AEs related to administration of these therapies or procedures must also be documented on the appropriate CRF.

8.10.1 Concomitant Therapy

A concomitant therapy is any non-protocol specified drug or substance (including over-the-counter medications, herbal medications and vitamin supplements) administered between signing informed consent and completion of the post-treatment follow-up period. All concomitant medications/treatments and significant non-drug therapies (including supplements and assistive devices) received by a patient, including changes in the patient's current medications, must be recorded in the patient's source documents and CRF. Patients taking over the counter (OTC) omega-3 fatty acids should make every effort to remain on the same brand throughout the study.

Allowed Concomitant Therapy

Any medications deemed necessary by the Investigator are allowed except those listed in the disallowed concomitant therapy.

Disallowed Concomitant Therapy

No lipid lowering therapies (e.g., fibrates, niacin, fish oil or other products containing omega-3 fatty acids [including OTC preparations]), -glucagon-like peptide-1 (GLP-1) agonists, Glybera, or systemic corticosteroids may be started or adjusted after baseline qualification. Doses of existing oral anti-diabetic medication, oral contraceptives, hormone replacement therapy, anticoagulants, or drugs or dietary supplements with potential lipid-altering effects should not be adjusted. Study patients are prohibited from receiving other experimental agents during the study. This includes marketed agents at experimental dosages that are being tested for the treatment of hypertriglyceridemia.

Patients should consult with the Site Investigator or designee prior to initiating any new medication, including non-prescription or herbal compounds or any other non-drug therapy.

8.10.2 Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between signing of informed consent and Week 65 (or Week 117 if patient enters the extended treatment period) visit.

Disallowed Concomitant Procedure

Plasma apheresis is not allowed during the study.

8.11 Treatment Compliance

Compliance with treatment dosing is to be monitored and recorded by Study Center staff. The Study Center staff is required to document the receipt, dispensing, and return/destruction of volanesorsen. Patients that are self-administering volanesorsen at home must record treatment in a dosing diary that will be reviewed periodically by Study Center staff and the Clinical Monitor.

9. SERIOUS AND NON-SERIOUS ADVERSE EVENT REPORTING

9.1 Sponsor Review of Safety Information

Safety information will be collected, reviewed, and evaluated by the Sponsor in accordance with the Safety Management Plan throughout the conduct of the clinical trial.

9.2 Regulatory Requirements

The Sponsor is responsible for regulatory submissions and reporting to the Investigators of serious adverse events (SAEs) including suspected unexpected serious adverse reactions (SUSARs) per the International Conference on Harmonization (ICH) guidelines E2A and ICH E6. Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines.

Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) will be notified of any SAE according to applicable regulations. The Independent DSMB will be notified of any SAE as specified in the DSMB charter.

In addition to the Investigator's assessment of relatedness, the Sponsor or designee will evaluate the available information and perform an independent assessment of relatedness. While the Sponsor may upgrade an Investigator's decision it is not permissible to downgrade the Investigator's opinion for the purposes of determining whether the SAE meets the definition of a SUSAR.

The following table identifies the SAEs that the Sponsor or designee will not report on an individual basis in an expedited manner because they are anticipated to occur in the study population independent of volanesorsen exposure. The Investigator still has the responsibility to report all SAEs to the Sponsor as described in Sections 9.4.1 to 9.4.3.5.

Table 4 Expected Event for the Protocol Defined Population by Preferred Term and the Expected Incidence

Preferred Term	Expected Incidence in the Protocol Defined Population (Gaudet et al. 2010 and 2013)
Pancreatitis associated events including the PTs of hereditary pancreatitis, pancreatitis, pancreatitis acute, pancreatitis chronic, pancreatitis necrotizing, pancreatitis relapsing	0.2-0.35 events per patient-year

Fatal pancreatitis associated events will be considered as unexpected and are reportable. The Sponsor and DSMB will monitor non-fatal pancreatitis associated SAEs using the incidence rate of the event compared to the rate expected in a non-volanesorsen exposed population. If the aggregate analysis indicates that an event is occurring significantly more frequently or at a greater severity than expected, then the event will be reported.

SAEs not specified in the table will be evaluated on case by case basis to determine whether there is a reasonable possibility that the drug caused the event. If the event is considered by the Sponsor or designee to meet the definition of a SUSAR the event will be reported.

9.3 Definitions

9.3.1 Adverse Event

An adverse event is any unfavorable and unintended sign (including a clinically-significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the study or use of investigational drug product, whether or not the AE is considered related to the investigational drug product.

9.3.2 Adverse Reaction and Suspected Adverse Reaction

An adverse reaction is any adverse event caused by volanesorsen.

A suspected adverse reaction is any adverse event for which there is a reasonable possibility that volanesorsen drug caused the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

9.3.3 Serious Adverse Event (SAE)

A serious adverse event is any adverse event that in the view of either the Investigator or Sponsor, meets any of the following criteria:

- Results in death
- Is life threatening: that is, poses an immediate risk of death at the time of the event

An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Hospitalization is defined as an admission of greater than 24 hours to a medical facility and does not always qualify as an AE
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly or birth defect in the offspring of the patient (whether the patient is male or female)
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

9.4 Monitoring and Recording Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the study (i.e., before informed consent) should be recorded as Medical History and not recorded as AEs unless the pre-existing condition worsened. The Investigator should always group signs and symptoms into a single term that constitutes a **single unifying diagnosis** if possible.

9.4.1 Serious Adverse Events

In the interest of patient safety, and in order to fulfill regulatory requirements**,** all SAEs (regardless of their relationship to volanesorsen) should be reported to the Sponsor or designee within 24 hours of the Study Center's first knowledge of the event. The collection of SAEs will begin after the patient signs the informed consent form and stop at the end of the patient's follow-up period which is defined as the Week 65 visit (or Week 117 if patient enters the extended treatment period). When the Investigator is reporting by telephone, it is important to speak to someone in person versus leaving a message. An Initial Serious Adverse Event Form should be completed and a copy should be faxed to the Sponsor or designee.

Detailed information should be actively sought and included on Follow-Up Serious Adverse Event Forms as soon as additional information becomes available. All SAEs will be followed until resolution. SAEs that remain ongoing past the patient's last protocol-specified follow-up visit will be evaluated by the Investigator and Sponsor. If the Investigator and Sponsor agree the patient's condition is unlikely to resolve, the Investigator and Sponsor will determine the follow-up requirement.

9.4.2 Non-Serious Adverse Events

The recording of non-serious AEs will begin after the patient signs the informed consent form and will stop at the end of the patient's follow-up period, which is defined as the Week 65 visit (or Week 117 if patient enters the extended treatment period). The Investigator will monitor each patient closely and record all observed or volunteered AEs on the Adverse Event Case Report Form.

9.4.3 Evaluation of Adverse Events (Serious and Non-Serious)

The Investigator's opinion of the following should be documented on the Adverse Event Case Report Form:

9.4.3.1 Relationship to the Study Drug

The event's relationship to volanesorsen is characterized by 1 of the following:

- **Related:** There is clear evidence that the event is related to the use of volanesorsen, e.g., confirmation by positive rechallenge test
- **Possible:** The event cannot be explained by the patient's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and volanesorsen administration

- **Unlikely/Remote:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to volanesorsen administration and/or exposure suggests that a causal relationship is unlikely (For reporting purposes, Unlikely/Remote will be grouped together with Not Related)
- **Not Related:** The event can be readily explained by the patient's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and volanesorsen

9.4.3.2 Severity

The severity of AEs and SAEs will be graded based on criteria from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010 (refer to Appendix D). Any AE not listed in Appendix D will be graded as follows:

- **Mild:** The event is easily tolerated by the patient and does not affect the patient's usual daily activities
- **Moderate:** The event causes the patient more discomfort and interrupts the patient's usual daily activities
- **Severe:** The event is incapacitating and causes considerable interference with the patient's usual daily activities

If the event is an SAE, then all applicable seriousness criteria must be indicated (criteria listed in Section 9.3.3).

9.4.3.3 Action Taken with Volanesorsen

Action taken with volanesorsen due to the event is characterized by 1 of the following:

- **None:** No changes were made to volanesorsen administration and dose
- **Permanently Discontinued:** Volanesorsen was discontinued and not restarted
- **Temporarily Interrupted, restarted – same dose:** Dosing was temporarily interrupted or delayed due to the AE and restarted at the same dose
- **Reduced schedule:** Dosing frequency was reduced

9.4.3.4 Treatment Given for Adverse Event

Any treatment (e.g., medications or procedures) given for the AE should be recorded on the Adverse Event Case Report Form (treatment should also be recorded on the concomitant treatment or ancillary procedures CRF as appropriate).

9.4.3.5 Outcome of the Adverse Event

If the event is a non-serious AE then the event's outcome is characterized by 1 of the following:

- **AE Persists:** Patient terminates from the trial and the AE continues
- **Recovered:** Patient recovered completely from the AE

- **Became Serious:** The event became serious (the date that the event became serious should be recorded as the Resolution Date of that AE and the Onset Date of the corresponding SAE)
- **Change in Severity** (if applicable): AE severity changed

If the event is a SAE then the event's outcome is characterized by 1 of the following:

- **Ongoing:** SAE continuing
- **Persists (as non-serious AE):** Patient has not fully recovered but the event no longer meets serious criteria and should be captured as an AE on the non-serious AE eCRF (the SAE resolution date should be entered as the date of onset of that AE)
- **Recovered:** Patient recovered completely from the SAE (the date of recovery should be entered as the SAE resolution date)
- **Fatal:** Patient died (the date of death should be entered as the SAE resolution date)

9.4.4 Adjudication Committees

All SAEs that occur during the study that are consistent with a major acute cardiovascular event (MACE) will be adjudicated by a blinded, independent committee as outlined in the MACE Adjudication Charter.

All AEs and SAEs that occur during the study that are consistent with an event of acute pancreatitis will be adjudicated by a blinded, independent committee according to the Atlanta classification of acute pancreatitis (Banks et al. 2013) and as outlined in the Pancreatitis Adjudication Charter. In addition, data for prior episodes of acute pancreatitis or suspected pancreatitis will be collected by review of each patient's medical chart and these events will also be adjudicated.

9.5 Procedures for Handling Special Situations

9.5.1 Abnormalities of Laboratory Tests

Clinically-significant abnormal laboratory test results may, in the opinion of the Investigator, constitute or be associated with an AE. Examples of these include abnormal laboratory results that are associated with symptoms, or require treatment, e.g., bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac arrhythmias due to hyperkalemia. Whenever possible, the underlying diagnosis should be listed in preference to abnormal laboratory values as AEs. Clinically-significant abnormalities will be monitored by the Investigator until the parameter returns to its baseline value or until agreement is reached between the Investigator and Sponsor Medical Monitor. Laboratory abnormalities deemed not clinically-significant (NCS) by the Investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator should not be deemed NCS on the laboratory sheet.

The Investigator is responsible for reviewing and signing all laboratory reports. The signed clinical laboratory reports will serve as source documents and should include the Investigator's assessment of clinical significance of out of range/abnormal laboratory values.

9.5.2 Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the patient is hospitalized; the Study Center must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the patient's consent to participate in the study
- The condition that required the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the patient's consent to participate in the study and the timing of the procedure or treatment
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission

9.5.3 Dosing Errors

Volanesorsen dosing errors should be documented as Protocol Deviations. A brief description should be provided in the deviation, including whether the patient was symptomatic (list symptoms) or asymptomatic, and the event accidental or intentional.

Dosing details should be captured on the Dosing Case Report Form. If the patient takes a dose of volanesorsen that exceeds protocol specifications and the patient is symptomatic, then the symptom(s) should be documented as an AE and be reported per Section 9.4.

Should an overdose occur, the Investigator or designee should refer to the Guidance to Investigator's section of the Investigator's Brochure and contact the Sponsor or designee within 24 hours.

9.5.4 Contraception and Pregnancy

Male patients and female patients of childbearing potential must continue to use appropriate contraception with their partners, or refrain from sexual activity, as described in Section 6.3.1.

If a patient becomes pregnant or a pregnancy is suspected, or if a male patient makes or believes that he has made someone pregnant during the study, then the Study Center staff must be informed immediately. An Initial Pregnancy Form should be submitted to the Sponsor or designee **within 24 hours** of first learning of the occurrence of pregnancy. Follow-up information including delivery or termination is reported on Follow-up Pregnancy Forms and reported within 24 hours.

Payment for all aspects of obstetrical care, child or related care will be the patient's responsibility.

Female patients: If a suspected pregnancy occurs while on the study (including follow-up), a pregnancy test will be performed. The patient with a confirmed pregnancy will be immediately withdrawn from treatment with volanesorsen. However, the patient will be encouraged to complete the post-treatment follow-up portion of the study to the extent that study procedures do not interfere with the pregnancy. Regardless of continued study participation, the study

physician will assist the patient in getting obstetrical care and the progress of the pregnancy will be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the Study Center and Sponsor may require access to the mother and infant's medical records for an additional 8 weeks after birth.

Male patients: The progress of the pregnancy in a male patient's partner should be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, **the Study Center and Sponsor may request access to the mother and infant's medical records for an additional 8 weeks after birth**. Follow-up will be performed to the extent permitted by applicable regulations and privacy considerations.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints

For fasting lipid measurements, the values at Month 3 analysis time point are defined as the average of Week 12 (Day 78) and Week 13 (Day 85) fasting assessments, the values of Month 6 analysis time point is at the end of Month 6 are defined as the average of Week 25 (Day 169) and Week 26 (Day 176) fasting assessments, and the values at the Month 12 analysis time point are defined as the average of Week 50 (Day 344) and Week 52 (Day 358) fasting assessments.

10.1.1 Efficacy Endpoints

- Percent change and absolute change from baseline in fasting TG
- Frequency and severity of patient reported abdominal pain during the treatment period
- Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-HDL-C, apoB, HDL-C, apolipoprotein A-1 (apoA-1), VLDL-C, and LDL-C
- Percent change from baseline in fasting total apolipoprotein C-III
- Change in blood viscosity (may be evaluated)
- Quality of Life questionnaires (EQ-5D, SF-36)
- Adjudicated acute pancreatitis event rate
- Other symptoms: eruptive xanthoma, lipemia retinalis

10.1.2 Safety Endpoints

- Adverse events including adjudicated events of pancreatitis and MACE
- Vital signs and weight
- Physical examinations
- Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis)
- Echocardiography

- Electrocardiograms (ECGs)
- Use of concomitant medications
- MRIs
- Platelet aggregation (may be evaluated)

10.2 Sample Size

No sample size calculations were performed as this is an open-label study.

10.3 Populations

Full Analysis Set (FAS): All patients who are enrolled and received at least 1 dose of active Study Drug and have a baseline TG assessment. The FAS represents the practically-feasible intent-to-treat (ITT) population as delineated in ICH Guideline E9.

Per Protocol Set (PPS): Subset of the FAS who received 9 of first 13 scheduled doses of volanesorsen and with no significant protocol deviations that would be expected to affect efficacy and PD assessments. The detailed criteria will be specified and finalized prior to the final database lock.

Safety Set: All patients who are enrolled and receive at least 1 dose of volanesorsen.

PK Population: All patients who are enrolled, receive at least 1 dose of volanesorsen, and have at least 1 post first dose PK sample collected, analyzed, and reported.

10.4 Definition of Baseline

Definitions of baseline are given below for the purposes of the final analysis.

For fasting lipid measurements, 2 baselines are defined for each patient in Groups 1 and 2: Group 1 (ISIS 304801-CS6) or Group 2 (ISIS 304801-CS16) index study baseline and the baseline in this open-label study, which is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 (e.g., qualification assessments or assessments from final visit of the ISIS 304801-CS6 or ISIS 304801-CS16 index studies if used for qualification).

For other measurements, baseline for patients on active treatment in the ISIS 304801-CS6 or ISIS 304801-CS16 index study will be the ISIS 304801-CS6 or ISIS 304801-CS16 index study baseline. For patients on placebo in the ISIS 304801-CS6 or ISIS 304801-CS16 index study, baseline will be the last non-missing assessment prior to the first dose of Study Drug.

10.5 Interim Analysis

An interim analysis may be conducted after the last patient's Week 13 visit of the open-label study or after the database of the ISIS 304801-CS6 and ISIS 304801-CS16 index studies are locked and unblinded. Both safety and efficacy information from this open-label study may be summarized during this interim analysis. Efficacy analyses will be detailed in the SAP.

10.6 Planned Methods of Analysis

All eCRF data, lab data transfers, as well as any outcomes derived from the data, will be provided in the patient data listings. Patient data listings will be presented for all patients enrolled into the study. Descriptive summary statistics including n, mean, median, standard deviation, standard error, interquartile range (25th percentile, 75th percentile), and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data by treatment group of the index studies for patients on active in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies, and pooled treatment naive group which including patients on placebo in index studies. Where appropriate, p-values will be reported. All statistical tests will be conducted using 2-sided tests with 5% Type I error rates unless otherwise stated.

TG related endpoints will be assessed in the FAS and PPS, and all other efficacy endpoints will be assessed in the FAS. All safety assessments will be performed on the Safety Set. PK endpoints will be assessed in the PK Set as applicable.

10.6.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics by treatment group and overall. The patient disposition will be summarized by treatment group and overall. All patients enrolled will be included in a summary of patient disposition.

10.6.2 Safety Analysis

Treatment duration and amount of Study Drug received will be summarized by treatment group and overall.

Patient incidence rates of AEs will be tabulated by MedDRA system organ class, MedDRA preferred term, and treatment group of the index studies. Narratives of treatment-emergent deaths, serious and significant AEs, including early withdrawals due to AEs, will also be provided.

All treatment-emergent AEs, all treatment-emergent AEs potentially related to Study Drug, all treatment-emergent serious AEs, and all treatment-emergent serious AEs potentially related to Study Drug will be summarized.

Injection Site Reactions (ISRs) will be summarized by treatment group, MedDRA preferred term and severity.

Independently adjudicated events of MACE and pancreatitis will be summarized by treatment group.

Laboratory tests to ensure patient safety including chemistry panel, complete blood count (CBC) with differential, coagulation panel, IM, complement etc., will be summarized by study visits by treatment group.

These safety variables will also be presented as change and percent change from baseline over time after Study Drug administration, as appropriate.

Vital signs, weight, ECG measures, echocardiography assessments, and MRI assessments will be tabulated by treatment group.

10.6.3 Efficacy Analysis

Percent change and change from baseline to Month 3, Month 6, and Month 12 in fasting TG will be summarized by treatment group. Response rate of patients with fasting plasma TG < 750 mg/dL or achieving fasting TG ≥ 40% reduction from baseline at Month 3, Month 6, and Month 12 will be summarized. Response analysis will also be conducted using a range of fasting plasma TG thresholds for determination of responder status.

Percent change and change from baseline to Month 3, Month 6, and Month 12 will also be summarized by treatment group for other fasting lipid measures including non-HDL-C, apoB, HDL-C, apoA-1, VLDL-C, and LDL-C, total cholesterol, and fasting total apoC-III.

The incremental effects of volanesorsen on lipid measures will be explored and the association between changes in lipid parameters and total amount of drug received will be examined, as appropriate.

Frequency and severity of patient reported abdominal pain, adjudicated acute pancreatitis event rate, quality of life assessments, and comparison of other symptoms including eruptive xanthomas and lipemia retinalis will be summarized by treatment group.

Additional details of the analyses to be conducted will be provided in the SAP.

10.6.4 Pharmacokinetic and Immunogenicity Analysis

10.6.4.1 Pharmacokinetic Analysis

For all patients, pre-dose and post-treatment volanesorsen plasma concentrations will be summarized using descriptive statistics by treatment group and IM status.

For patients in the PK subgroup only, non-compartmental PK analysis of volanesorsen will be carried out on each individual patient data set using data collected in the open-label study from the intensive PK subgroup, following a single-dose (i.e., single-dose PK) or multiple doses (i.e., steady-state PK), depending on their earlier treatment in the index studies (Group 1 and 2 patients). On Week 1 Day 1 of the open-label study, patients who received placebo in the index study will receive the first treatment of volanesorsen (single-dose PK), while patients who received volanesorsen in the index studies had been on volanesorsen treatment for 12 months (ISIS 304801-CS6) or 6 months (ISIS 304801-CS16), thus the PK data collected from these patients reflect steady-state PK. The maximum observed drug concentration (C_{max}) and the time taken to reach C_{max} (T_{max}) will be obtained directly from the concentration-time data. Area under the plasma concentration-time curve from time zero to 24 hours (AUC_{0-24h}) will be calculated using the linear trapezoidal rule. Apparent systemic (plasma) clearance after SC administration (CL_{0-24h} /F) will be calculated from CL_{0-24h}/F = Actual Dose/AUC_{0-24h}. Mean residence time (MRT) from time zero to 24 hours after the SC administration will be calculated from the equation, $MRT_{0-24h} = AUMC_{0-24h}/AUC_{0-24h}$, where $AUMC_{0-24h}$ is the area under the moment plasma concentration-time curve from time zero to 24 hours after the SC administration. Other PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist.

Plasma PK parameters will be summarized using descriptive statistics by treatment group and IM status. Additional details regarding the PK analysis will be described in the SAP.

Population PK, PK/PD, and covariate analysis may be performed if deemed appropriate, and results will be reported separately.

10.6.4.2 Immunogenicity Analysis

Immunogenicity (IM) results (screen positive/negative, confirmed positive/negative or not evaluable, and when applicable, titer of anti-volanesorsen antibodies) before, during, and after treatment with Study Drug (volanesorsen) (i.e., sample [anti-drug antibody] ADA status) will be listed by their prior treatment in study ISIS 304801-CS6 or ISIS 304801-CS16 (Groups 1 and 2) and study day. Subject ADA status (positive/negative or not evaluable) for all evaluable patients, along with the study day associated with the first positive IM status emerged (T_{first}, i.e., onset of ADA development), the last positive IM status observed (T_{last}), the last ADA sample collection day, and subject - peak titer if applicable, will be listed by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16 (Groups 1 and 2) and study day. Subjects with positive anti-volanesorsen antibody status may be further classified (when applicable) as being either 'persistent', 'transient', or 'not determinable', if deemed appropriate.

Additionally, the sample and subject IM incidence (number) and incidence rate (percent) will be summarized as the total number and percent of evaluated subjects with antibody negative, positive, and unknown status by treatment group. Furthermore, onset and titer of the ADA response, if applicable, will be summarized as median, quartiles (25% and 75%), and range.

Additional details regarding the IM data analysis will be described in the SAP.

Potential relationships between immunogenicity results (e.g., IM status) and selected efficacy (e.g., % change in fasting TG from baseline at 3-, 6-, and 12-month endpoints), safety, and PK (e.g., C_{trough}) measures will be evaluated using graphical analysis and statistical analysis. These analyses will be either conducted and included in the study report, or data pooled and analyzed from all available Phase 2 and 3 studies and reported separately.

11. INVESTIGATOR'S REGULATORY OBLIGATIONS

11.1 Informed Consent

The written informed consent document should be prepared in the language(s) of the potential patient population, based on an English version provided by the Sponsor.

Before a patient's participation in the trial, the Investigator is responsible for obtaining written informed consent from the patient after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific qualification procedures or any Study Drug are administered. The patient must be given sufficient time to consider whether to participate in the study.

The acquisition of informed consent and the patient's agreement or refusal to notify his/her primary care physician should be documented in the patient's medical records and the informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion (not necessarily an Investigator). The original signed

informed consent form should be retained in the Study Master File and in any other locations required by institutional policy, and a copy of the signed consent form should be provided to the patient.

11.2 Ethical Conduct of the Study

The Guidelines of the World Medical Association (WMA) Declaration of Helsinki dated October 2002 the applicable regulations and guidelines of current Good Clinical Practice (GCP) as well as the demands of national drug and data protection laws and other applicable regulatory requirements will be strictly followed.

11.3 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent form, other written patient information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by the Sponsor before recruitment of patients into the study and shipment of volanesorsen. A copy of the written approval of any other items/materials that must be approved by the Study Center or IEC/IRB must also be received by the Sponsor before recruitment of patients into the study and shipment of Study Drug. The Investigator's Brochure must be submitted to the IEC/IRB for acknowledgement.

The Investigator must submit to and, where necessary, obtain approval from the IEC/IRB, for all subsequent protocol amendments and changes to the informed consent document. The Investigator should notify the IEC/IRB of deviations from the protocol in accordance with ICH GCP Section 4.5.2. The Investigator should also notify the IEC/IRB of serious adverse events occurring at the Study Center and other adverse event reports received from the Sponsor, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study. Copies of the Investigator's reports, all IEC/IRB submissions and the IEC/IRB continuance of approval must be sent to the Sponsor.

11.4 Patient Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained. On the case report forms (CRF) or other documents submitted to the Sponsor, patients should be identified by unique initials and a patient study number only. Documents that are not for submission to the Sponsor (e.g., signed informed consent forms) should be kept in strict confidence by the Investigator.

In compliance with Federal and local regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the patient to permit named representatives to have access to his/her study-related records without violating the confidentiality of the patient.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments

Protocol amendments must be made only with the prior approval of the Sponsor. Agreement from the Investigator must be obtained for all protocol amendments and amendments to the informed consent document. The regulatory authority and IEC/IRB must be informed of all amendments and give approval for any amendments likely to affect the safety of the patients or the conduct of the trial. The Investigator **must** send a copy of the approval letter from the IEC/IRB to the Sponsor.

12.2 Study Termination

The Sponsor reserves the right to terminate the study according to the terms of the site contract. The Investigator reserves the right to terminate their participation in the study, according to the terms of the site contract. The Investigator/Sponsor should notify the IEC/IRB in writing of the trial's completion or early termination and send a copy of the notification to the Sponsor.

12.3 Study Documentation and Storage

An electronic case report form (eCRF) utilizing an Electronic Data Capture (EDC) application will be used for this study.

The Investigator should ensure that all appropriately qualified persons to whom he/she has delegated trial duties are recorded on a Sponsor-approved Delegation of Site Responsibilities Form.

Source documents are original documents, data, and records from which the patient's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, imaging, and correspondence. In this study, CRFs may not be used as source documents.

The Investigator and Study Center staffs are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation in accordance with Section 8 of the ICH Guidelines (E6), suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Elements should include:

- Patient files containing completed CRFs, informed consents, and supporting copies of source documentation
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation and all correspondence to and from the IEC/IRB and the Sponsor
- If volanesorsen supplies are maintained at the Study Center, proof of receipt, volanesorsen Accountability Record, Return of volanesorsen for Destruction, final study volanesorsen reconciliation, and all volanesorsen-related correspondence

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

No study document should be destroyed without prior written agreement between the Sponsor or and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor.

12.4 Study Monitoring

The Sponsor representative and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the trial (e.g., CRFs and other pertinent data) provided that patient confidentiality is respected.

The Sponsor monitor is responsible for inspecting the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to patient medical records and other study-related records needed to verify the entries on the CRFs.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's Clinical Quality Assurance Department. Inspection of Study Center facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the trial conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

To ensure the quality of clinical data a clinical data management review will be performed on patient data received by the Sponsor. During this review, patient data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or Study Center notifications will be sent to the Study Center for completion and return to Sponsor.

The Principal Investigator will sign and date the indicated places on the CRF. These signatures will indicate that the principal Investigator inspected or reviewed the data on the CRF, the data queries, and the Study Center notifications, and agrees with the content.

12.5 Language

Case report forms must be completed in English. Generic names for concomitant medications should be recorded in English if possible, unless it is a combination drug, then record the trade name in English.

All written information and other material to be used by patients and investigative staff must use vocabulary and language that are clearly understood.

12.6 Compensation for Injury

The Sponsor maintains appropriate insurance coverage for clinical trials and will follow applicable local compensation laws. Patients will be treated and/or compensated for any study-related illness/injury in accordance with the information provided in the Compensation for Injury section of the Informed Consent document.

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14. APPENDICES

Appendix A Schedule of Procedures

Appendix A Schedule of Procedures

Study Period		Qual[a]	Treatment Period																						Post Treatment Follow-up		
Study Week		-2 to -1	Wk 1		Wk 4	Wk 6	Wk 8	Wk 10	Month 3		Wk 15 & 17	Wk 19	Wk 21 & 23	Month 6		Wk 28 & 30	Wk 32	Wk 34 & 36	Wk 38	Wk 40 & 42	Wk 44	Wk 46 & 48	Month 12		Wk 54 & 56	Wk 58	Wk 65
									Wk 12	Wk 13				Wk 25	Wk 26								Wk 50	Wk 52 or ET			
Study Day		-14 to -7	1	2	22	36	50	64	78	85	99 & 113	127	141 & 155	169	176	190 & 204	218	232 & 246	260	274 & 288	302	316 & 330	344	358	372 & 386	400	449
Visit Window+/- Days		0	0	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	7	7
Informed Consent		X																									
Outpatient Visit		X	X	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X	X[l]	X[l]	X[l]	X[l]	X	X[l]	X[l]	X[l]	X	X[l]	X[l]	X[l]	X[l]	X	X[l]	X[l]	X
Inclusion/Exclusion Criteria		X																									
Medical History[b]																											
Vital Signs + body weight (+ height on Day 1 only)		X	X		X		X			X					X				X					X			X
Physical Examination			X							X					X				X					X			X
12- lead ECG (triplicate)										X					X				X					X			X
MRI (liver/spleen)																								X[m]			
Echocardiography															X[m]									X[m]			
Blood Draw (Fasting)[d]	Chemistry Panel	X	X		X		X			X		X			X		X		X		X			X		X	X
	CBC with Differential[c]	X	← X → Platelets are assessed each calendar week, visits do not have specified windows to allow flexibility of scheduling.																								X
	Serum Lipid Panel	X	X		X		X		X	X				X	X				X				X	X			X
	Blood viscosity[e]		X							X					X									X			
	Platelet aggregation[e]	X	X							X					X									X			
	Coagulation (aPTT, PT, INR)	X					X			X					X				X					X			
	hsCRP, HbA1c, FPG, and de-lipidated free glycerol		X							X					X									X			X
	Sedimentation Rate		X							X					X									X			X
	Complement (C5a, Bb)		X							X					X									X			X
	Troponin I		X							X					X									X			X
	Platelet Bound Autoantibodies[e]		X																								
	Plasma PK - Volanesorsen		X[n]	X	X		X			X					X				X					X			X
	Anti-Volanesorsen Antibodies		X		X		X			X					X				X					X			X
	Serum Pregnancy Test[f]	X			X		X			X		X			X		X		X		X			X		X	X

Appendix A Schedule of Procedures *Continued*

Study Period		Qual[a]	Treatment Period																							Post Treatment Follow-up		
Study Week		-2 to -1	Wk 1		Wk 4	Wk 6	Wk 8	Wk 10	Month 3		Wk 15 & 17	Wk 19	Wk 21 & 23	Month 6		Wk 28 & 30	Wk 32	Wk 34 & 36	Wk 38	Wk 40 & 42	Wk 44	Wk 46 & 48	Month 12		Wk 54 & 56	Wk 58	Wk 65
									Wk 12	Wk 13				Wk 25	Wk 26								Wk 50	Wk 52 or ET			
Study Day		-14 to -7	1	2	22	36	50	64	78	85	99 & 113	127	141 & 155	169	176	190 & 204	218	232 & 246	260	274 & 288	302	316 & 330	344	358	372 & 386	400	449
Visit Window+/- Days		0	0	0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	7	7
Blood Draw (Fasting)[d]	Archive blood sample for potential gene sequencing related to hypertriglyceridemia (Group 2 if not available from index study)[i]	X	X																								
	Archived Serum & Plasma Samples[g]		X				X			X					X									X			X
Urinalysis[d]		X	X°		X		X			X°		X°			X°		X°		X°		X°			X°		X°	X°
Fundus Photography[h]		X																						X[m]			
Genetic testing for FCS diagnosis (if not available in medical history)[i]		X																									
Weekly Study Drug: SC Injection			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Symptom Diary (weekly)		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Assessment(s)			X							X					X									X			X
Food/Drink Diary (quarterly)[j]			X							X					X									X			X
Diet/Alcohol Counseling[k]		X	X		X		X			X					X				X					X		X	X
Adverse Events		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a Qualification procedures performed (Please refer to Sections 3.4.1, 4.1, and 6.1.1)

b Patient charts will be reviewed in order to collect data for events of acute pancreatitis or suspected pancreatitis in the patient's medical history. Chart review may be conducted at any time during the study. These events will be adjudicated in the same manner as for events of pancreatitis during the study

c Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1 week and the result must be reviewed by the Investigator and confirmed to be acceptable before dosing can continue. All platelet count results will be promptly reviewed by the Investigator to determine if the count has met a stopping rule, or the dose reduction rule of 100,000/mm^3, or the dose pause rule of 75,000/mm^3. Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor

Appendix A Schedule of Procedures *Continued*

Legend Text *Continued*

d Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours. During treatment period urine and blood samples will be collected prior to Study Drug administration. Does not apply to 24-hour PK blood draw

e May be done. Blood viscosity and platelet aggregation in volanesorsen-treatment naïve patients only

f Females of childbearing potential only

g Serum and plasma samples will be collected and stored for follow-up exploration of laboratory findings and/or adverse events (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.) in this or subsequent clinical studies of volanesorsen

h If possible, fundus photography should be completed prior to administration of the first dose of Study Drug (Group 2 [ISIS 304801-CS16 roll-over patients]) and repeated at Week 52 (Please refer to Section 6.2.2.2)

i Genetic testing can be conducted for study qualification (Group 2 [ISIS 304801-CS16 roll-over patients]); genetic testing will only be conducted if allowed in the geographic region and only after the patient has given specific written informed consent for genetic testing

j In addition to diary, patients will be contacted at random times during the study to review their current eating and drinking habits

k To reinforce compliance to the diet and alcohol restrictions. Random diet/alcohol assessments (phone visits) will also be performed by dietician or study personnel

l Assessments and procedures to be conducted by either a home healthcare nurse, or the Study Center as arranged by the Study Center personnel

m A ± 7-day window is allowed for MRI, echocardiography procedures and fundus photography

n Full or abbreviated PK profile (see Appendix C)

o Expanded urinalysis (see Appendix B)

Appendix A Schedule of Procedures – Extended Treatment Period

Study Period		Treatment Period																Post-Treatment Follow-up		
Study Week		**Wk 54 & 56**	**Wk 58**	**Wk 60 & 62**	**Mo 15 Wk 64**	**Wk 66 & 68**	**Wk 70**	**Wk 72 & 74**	**Mo 18 Wk 76**	**Wk 78 & 80**	**Wk 82**	**Wk 84, 86, & 88**	**Mo 21 Wk 90**	**Wk 92 & 94**	**Wk 96**	**Wk 98, 100 & 102**	**Mo 24 Wk 104**	**Wk 106 & 108**	**Wk 110**	**Mo 27 Wk 117**
Study Day		**372 & 386**	**400**	**414 & 428**	**442**	**456 & 470**	**484**	**498 & 512**	**526**	**540 & 554**	**568**	**582, 596 & 610**	**624**	**638 & 652**	**666**	**680, 694 & 708**	**722**	**736 & 750**	**764**	**813**
Visit Window+/- Days		**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**7**	**7**
Outpatient Visit		X[f]	X[f]	X[f]	X	X[f]	X[f]	X[f]	X	X[f]	X[f]	X[f]	X	X[f]	X[f]	X[f]	X	X[f]	X[f]	X
Vital Signs (+ body weight)					X				X				X				X			X
Physical Examination									X								X			
12- lead ECG (triplicate)									X								X			
Urinalysis(including P/C ratio)			X		X		X		X		X		X		X		X		X	X
Blood Draw (Fasting)[b]	Chemistry Panel		X		X		X		X		X		X		X		X		X	X
	CBC with Differential[a]	X Platelets are assessed each calendar week, visits do not have specified windows to allow flexibility of scheduling.																		X
	Serum Lipid Panel				X				X				X				X			X
	Coagulation (aPTT, PT, INR)				X				X				X				X			
	Troponin I				X				X				X				X			X
	Plasma PK - ISIS 304801[c]								X								X			X
	Anti-ISIS 304801 Antibodies								X								X			X
	Serum Pregnancy Test[d]		X		X		X		X		X		X		X		X		X	X
Weekly Study Drug: SC Injection		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Diet/Alcohol Counseling[e]					X				X				X				X			
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Appendix A Schedule of Procedures – Extended Treatment Period *Continued*

Legend Text

a Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1 week and the result must be reviewed by the Investigator and confirmed to be acceptable before dosing can continue. All platelet count results will be promptly reviewed by the Investigator to determine if the count has met a stopping rule, or the dose reduction rule of 100,000/mm^3, or the dose pause rule of 75,000/mm^3. Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor

b Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours. During treatment period urine and blood samples will be collected prior to Study Drug administration

c Abbreviated PK collection (see Appendix C)

d Females of childbearing potential only

e To reinforce compliance to the diet and alcohol restrictions

f Assessments and procedures to be conducted by either a home healthcare nurse, or the Study Center as arranged by the Study Center personnel

Appendix B List of Laboratory Analytes

Appendix B List of Laboratory Analytes

Based on emerging data from this or future studies, additional tests not listed below may be performed on stored samples to better characterize the profile of volanesorsen or other similar oligonucleotides.

Clinical Chemistry Panel

- Sodium
- Potassium
- Chloride
- Bicarbonate
- Total protein
- Albumin
- Calcium
- Magnesium
- Phosphorus
- Glucose
- BUN
- Creatinine
- Uric Acid
- Total bilirubin
- Direct (conjugated) bilirubin
- Indirect (unconjugated) bilirubin
- ALT
- AST
- Alkaline phosphatase

Coagulation

- aPTT (sec)
- PT (sec)
- INR

Lipid Panel

- Total Cholesterol
- LDL-C
- HDL-C
- Triglycerides
- Non-HDL-C
- VLDL-C
- apoA-1
- apoB
- apoC-III

Hematology

- Red blood cells
- Hemoglobin
- Hematocrit
- MCV, MCH, MCHC
- Platelets
- White blood cells
- WBC Differential (% and absolute)
  - Neutrophils
  - Eosinophils
  - Basophils
  - Lymphocytes
  - Monocytes

Pharmacokinetics[1] & Immunogenicity

- Volanesorsen levels in plasma
- Anti-volanesorsen antibodies in plasma

Other Assessments

- hsCRP
- Sedimentation Rate
- C5a, Bb
- Troponin I[2]
- CK-MB[2]
- Platelet Bound Autoantibodies[3]
- De-lipidated free glycerol
- HbA1c, FPG
- Blood viscosity[3]

Urinalysis

- Color
- Appearance
- Specific gravity
- pH
- Protein
- Blood
- Ketones
- Urobilinogen
- Glucose
- Bilirubin
- Leukocyte esterase
- Nitrate
- Microscopic examination[4]

Additional Measures for Expanded Urinalysis

- Total protein (quantitative)
- Microalbumin
- β2-microglobulin

Platelet Function

- Platelet aggregation[3]

1 Plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, IM testing (or possibly for purposes of IM assay development and/or validation), or to assess other actions of volanesorsen with plasma constituents

2 All abnormal troponin samples will be rerun at the central laboratory and also analyzed for CK-MB

3 May be done

4 Will be performed on abnormal findings unless otherwise specified

Appendix C Pharmacokinetic Sampling Schedule

Appendix C Pharmacokinetic Sampling Schedule

Blood samples for the determination of plasma volanesorsen concentrations will be collected prior to dosing, and at various times throughout the dosing and post-treatment follow-up period as noted in the tables below.

PK Sampling Schedule (All Patients except PK Subgroup)

Week	**Wk 1**	**Wk 4**	**Wk 8**	**Wk 13**	**Wk 26**	**Wk 38**	**Wk 52**	**Wk 65#**
Study Day	**D1**	**D22**	**D50**	**D85**	**D176**	**D260**	**D358**	**D449**
Visit Window +/- Days	0	2	2	2	2	3	2	7
Time Point	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime

Week 65 PK collection will be omitted for patients continuing to receive volanesorsen beyond Week 52

PK Sampling Schedule (PK Subgroup only*)

Week	**Wk 1**	**Wk 1**	**Wk 4**	**Wk 8**	**Wk 13**	**Wk 26**	**Wk 38**	**Wk 52**	**Wk 65#**
Study Day	**D1**	**D2**	**D22**	**D50**	**D85**	**D176**	**D260**	**D358**	**D449**
Visit Window +/- Days	0	0	2	2	2	2	3	2	7
Time Point	Pre-dose, 1, 2, 3, 4, 6, 8, and 12 hrs post-dose	24 hrs post-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime

* Patients at selected sites will be asked to participate in the extended 24-hour PK profile beginning on Study Day 1. Participation is optional

Week 65 PK collection will be omitted for patients continuing to receive volanesorsen beyond Week 52

PK Sampling Schedule (Extended Treatment Period)

Week	**Wk 76**	**Wk 104**	**Wk 117**
Study Day	**D526**	**D722**	**D813**
Visit Window +/- Days	2	2	7
Time Point	Pre-dose	Pre-dose	Anytime

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

The following grading recommendations for adverse events relating to lab test abnormalities are based upon the **Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010**

Adverse Event	Mild	Moderate	Severe
Hematology			
aPTT prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage
Eosinophils increased†	650 – 1,500 cell/mm^3	1,501 - 5,000 cell/mm^3	>5,000 cell/mm^3
Fibrinogen decreased	<1.0 - 0.75 x LLN or <25% decrease from baseline	<0.75 - 0.5 x LLN or 25 - <50% decrease from baseline	<0.5 x LLN or ≥50% decrease from baseline
Hemoglobin decreased (Anemia)	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated
Hemoglobin increased	Increase in >0 - 2 g/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 g/dL above ULN or above baseline if baseline is above ULN	Increase in >4 g/dL above ULN or above baseline if baseline is above ULN
INR increased	>1 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation
Lymphocyte count decreased	<LLN - 800/mm^3; <LLN - 0.8 x 10^9/L	<800 - 500/mm^3; <0.8 - 0.5 x 10^9 /L	<500 /mm^3; <0.5 x 10^9 /L
Lymphocyte count increased	-	>4000/mm^3 - 20,000/mm^3	>20,000/mm^3
Neutrophil count decreased	<LLN - 1500/mm^3; <LLN - 1.5 x 10^9 /L	<1500 - 1000/mm^3; <1.5 - 1.0 x 10^9 /L	<1000/mm^3; <1.0 x 10^9 /L
Platelet count decreased	<LLN - 75,000/mm^3; <LLN - 75.0 x 10^9 /L	<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9 /L	<50,000/mm^3; <50.0 x 10^9 /L
White blood cell decreased	<LLN - 3000/mm^3; <LLN - 3.0 x 10^9 /L	<3000 - 2000/mm^3; <3.0 - 2.0 x 10^9 /L	<2000/mm^3; <2.0 x 10^9 /L
Chemistry			
Acidosis	pH <normal, but >=7.3	-	pH <7.3
Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Alkalosis	pH >normal, but ≤7.5	-	pH >7.5
Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 x ULN
Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

Adverse Event	Mild	Moderate	Severe
Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer
CD4 lymphocytes decreased	<LLN - 500/mm^3; <LLN - 0.5 x 10^9 /L	<500 - 200/mm^3; <0.5 - 0.2 x 10^9 /L	<200/mm^3; <0.2 x 10^9 /L
CPK increased*	>ULN - <6 ULN	6 - 10 x ULN	>10 x ULN
Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 x ULN
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 mg/dL; >3.1 mmol/L; Ionized calcium >1.6 mmol/L; hospitalization indicated
Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 mg/dL; >13.9 mmol/L; hospitalization indicated
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0; hospitalization indicated
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 mg/dL; >1.23 mmol/L
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 mmol/L; hospitalization indicated
Hyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 mg/dL; <1.75 mmol/L; Ionized calcium <0.9 mmol/L; hospitalization indicated
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 mg/dL; <3.0 mmol/L	<40 mg/dL (<2.2 mmol/L) AND requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions‡
Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 mmol/L; hospitalization indicated
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 mg/dL; <0.4 mmol/L
Hyponatremia	<LLN - 130 mmol/L	-	<130 mmol/L
Hypophosphatemia	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 mg/dL; <0.6 mmol/L
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

Adverse Event	Mild	Moderate	Severe
Urine			
Proteinuria Adults Children	1+ proteinuria; urinary protein <1.0 g/24 hrs -	2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs; Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Urinary protein ≥3.5 g/24 hrs; Urine P/C >1.9
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated

[†]Grading for this parameter is derived from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007

*Grading for this parameter is derived from the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0, Nov 2014

[‡]Modified for consistency with the ADA and Endocrine Society Guidelines (Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. Diabetes Care 2013;36:1384-95)

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ISIS 304801-CS7

The APPROACH Open-Label Study

Volanesorsen (ISIS 304801)

An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol Amendment 6 – 18 November 2016

EudraCT No: 2015-003755-21

ISIS 304801-CS7

The APPROACH Open-Label Study

Volanesorsen (ISIS 304801)

An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol Amendment 6 – 18 November 2016

Protocol History:

Original Protocol:	28 August 2015
Protocol Amendment 1:	2 February 2016
Protocol Amendment 2:	22 April 2016
Protocol Amendment 3:	9 May 2016
Protocol Amendment 4:	6 June 2016
Protocol Amendment 5:	6 July 2016

Sponsor:

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[redacted]
MD, MBA
[redacted]

Ionis Protocol Number: ISIS 304801-CS7

Protocol Amendment 6

EudraCT No: 2015-003755-21

Clinical Phase: 3

The APPROACH Open-Label Study

Volanesorsen (ISIS 304801)

An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

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Date: 18 November 2016

Confidentiality Statement

This document contains confidential information of Ionis Pharmaceuticals, Inc., that must not be disclosed to anyone other than the recipient study staff and members of the independent ethics committee, institutional review board, or authorized regulatory agencies. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc.

Protocol Signature Page

Protocol Number: ISIS 304801-CS7

Protocol Title: An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Amendment: Amendment 6

Date: 18 November 2016

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)", dated 18 November 2016, and agree to conduct the study as described herein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice (E6).

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc.

Investigator's Signature

Investigator's Name *(please print)*

Date (DD Month YYYY)

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PROTOCOL AMENDMENT

Protocol Number: ISIS 304801-CS7

Protocol Title: An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Amendment Number: 6

Amendment Date: 18 November 2016

The purpose of this protocol amendment is to implement the following modifications to Protocol ISIS 304801-CS7 Amendment 5 dated 6 July 2016:

1. To allow patients who complete the 52-week treatment period to participate in an expanded access program or continue dosing for up to an additional 52 weeks until an expanded access program is approved and available in their country. Patients not participating in an expanded access program will enter the 13-week post treatment evaluation period.

2. The following assessments were added: Troponin I; labs to be performed in the event of a platelet count < 75,000/mm^3; platelet bound autoantibody testing at baseline (may be done); plus medical history, hepatitis B, C, and HIV at Screening (Group 3 patients).

Minor changes (not included in the list of changes below) have been made throughout the protocol to correct errors and/or to improve the overall clarity of the original protocol but these changes do not impact subject safety, exposure, or the overall study design.

The following table provides a summary list of major changes to the protocol:

Protocol Section	Description of Change	Rationale
Protocol Synopsis: Study Design Study Visit Schedule and Procedures 3.1 Study Design 6.1.6 Post-Treatment Period	**Was:** Following the Week 52 visit, patients will enter a 13-week post treatment evaluation period. **Is:** Following the Week 52 visit, patients will have the option of participating in an expanded access program or continuing dosing for up to an additional 52 weeks until an expanded access program is approved and available in their country. Patients not participating in an expanded access program will enter a 13-week post-treatment evaluation period.	To allow patients the option of continuing treatment with volanesorsen after completion of the 52-week open-label treatment period.

Protocol Section	Description of Change	Rationale

For consistency with the above changes:
appropriate wording was added to the following sections:

Protocol Synopsis: Study Visit Schedule and Procedures
Study Design and Treatment Schema
6.2.4 ECG
6.2.7 Disease Symptom Diary
6.2.8 Diet Monitoring
8.8.2 Follow-up Visits for Early Termination from Post-Treatment Follow-up Period
8.10.2 Concomitant Procedures
9.4.2 Non-Serious Adverse Events

and the following table and footnotes were added to Appendix A: Schedule of Procedures:

Appendix A Schedule of Procedures – Extended Treatment Period

Study Period		Treatment Period																Post-Treatment Follow-up		
Study Week		Wk 54 & 56	Wk 58	Wk 60 & 62	Mo 15 Wk 64	Wk 66 & 68	Wk 70	Wk 72 & 74	Mo 18 Wk 76	Wk 78 & 80	Wk 82	Wk 84, 86 & 88	Mo 21 Wk 90	Wk 92 & 94	Wk 96	Wk 98, 100 & 102	Mo 24 Wk 104	Wk 106 & 108	Wk 110	Mo 27 Wk 117
Study Day		372 & 386	400	414 & 428	442	456 & 470	484	498 & 512	526	540 & 554	568	582, 596 & 610	624	638 & 652	666	680, 694 & 708	722	736 & 750	764	813
Visit Window+/- Days		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	7	7
Outpatient Visit		X[f]	X[f]	X[f]	X	X[f]	X[f]	X[f]	X	X[f]	X[f]	X[f]	X	X[f]	X[f]	X[f]	X	X[f]	X[f]	X
Vital Signs (+ body weight)					X				X				X				X			X
Physical Examination									X								X			
12- lead ECG (triplicate)									X								X			
Urinalysis (including P/C ratio)			X		X		X		X		X		X		X		X		X	X
Blood Draw (Fasting)[b]	Chemistry Panel		X		X		X		X		X		X		X		X		X	X
	CBC with Differential[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Serum Lipid Panel				X				X				X				X			X
	Coagulation (aPTT, PT, INR)				X				X				X				X			
	Troponin I				X				X				X				X			X
	Plasma PK - ISIS 304801[c]								X								X			X
	Anti-ISIS 304801 Antibodies								X								X			X
	Serum Pregnancy Test[d]		X		X		X		X		X		X		X		X		X	X
Weekly Study Drug: SC Injection		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Diet/Alcohol Counseling[e]					X				X				X				X			
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

<table>
<tr><th>Protocol Section</th><th>Description of Change</th><th>Rationale</th></tr>
<tr><td colspan="3">

Appendix A Schedule of Procedures – Extended Treatment Period *Continued*

Legend Text

a Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1 week and determined not to have met a stopping rule before dosing can continue. If there is no reportable platelet count within 14 days of the last platelet count, the Investigator will contact the patient to hold dosing until a new platelet count is obtained and reviewed. All platelet count results will be promptly reviewed by the Investigator to ensure that the count has not met the stopping rule and to determine whether the rate of decline is suggestive that the patient could be approaching the dose pause rule of 75,000/mm^3. Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor

b Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours. During treatment period urine and blood samples will be collected prior to Study Drug administration

c Abbreviated PK collection (see Appendix C)

d Females of childbearing potential only

e To reinforce compliance to the diet and alcohol restrictions

f Assessments and procedures to be conducted by either a home healthcare nurse, or the Study Center as arranged by the Study Center personnel

and the following table and footnotes were added to Appendix C: Pharmacokinetic Sampling Schedule:

Week 65 PK collection will be omitted for patients continuing to receive volanesorsen beyond Week 52

PK Sampling Schedule: Extended Treatment Schedule

Week	**Wk 76**	**Wk 104**	**Wk 117**
Study Day	**D526**	**D722**	**D813**
Visit Window +/- Days	2	2	7
Time Point	Pre-dose	Pre-dose	Anytime

</td></tr>
<tr><td>6.1.4 Extended Treatment Period</td><td>**Added**

Patients will have the option of continuing dosing for up to an additional 52 weeks until an expanded access program is approved and available in their country.

During the extended treatment period, patients will report to the study center for clinic visits during Weeks 54-104 (see Schedule of Procedures in Appendix A). Study Drug will be administered once weekly unless the patient is on a biweekly dosing schedule for safety reasons (Section 8.1). Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), AEs, concomitant medication/procedure information, lipid panel, volanesorsen plasma concentrations, IM testing, ECGs, and physical examinations will be performed according to the schedule of procedures in Appendix A.</td><td>To outline the procedures to be performed during the extended treatment period.</td></tr>
</table>

<table>
<tr><th>Protocol Section</th><th>Description of Change</th><th>Rationale</th></tr>
<tr><td>6.1.4 Extended Treatment Period
Continued</td><td>Adverse events at the injection site should be collected as adverse events. Dietary counseling will be reinforced at intervals throughout the extended treatment period. All blood and urine samples should be collected prior to volanesorsen administration. Blood sampling at Weeks 54, 56, 58, 60, 62, 66, 68, 70, 72, 74, 78, 80, 82, 84, 86, 88, 92, 94, 96, 98, 100, and 102 may be conducted by a home healthcare nurse. Approval for study procedures to be conducted by a home healthcare nurse on other outpatient visit days will require prior approval by the Sponsor. Patients must be fasted prior to drawing all blood samples and samples drawn locally should also be sent to the central laboratory for analysis whenever possible. Every effort should be made to ensure the previous week's dose is given 7 days prior to a scheduled clinic visit. Dosing instructions and training will be provided to the patient where applicable.</td><td>To outline the procedures to be performed during the extended treatment period.</td></tr>
<tr><td>6.1.6 Post-Treatment Period</td><td>Added:
Patients who complete, or terminate early from, the extended treatment period without subsequently participating in an expanded access program will enter a 13-week post-treatment evaluation period consisting of 4 Study Center visits on Weeks 106, 108, and 110 (which may be conducted by a home healthcare nurse), and Week 117 as outlined in the Schedule of Procedures in Appendix A.</td><td>To describe the follow-up visits for patients that terminate early from the extended treatment period.</td></tr>
<tr><td>6.2.10 Chart Review for Incidents of Acute Pancreatitis in Medical History (Group 3)
Appendix A: Schedule of Procedures</td><td>Added:
Patient records will be reviewed for incidents of acute pancreatitis occurring up to 5 years prior to screening and information relating to these events will be collected for independent adjudication.</td><td>To collect acute pancreatitis medical history events on patients that did not participate in an index study (ISIS 304801-CS6 or ISIS 304801-CS16).</td></tr>
<tr><td>8.5.2 Safety Monitoring for Platelet Count Results</td><td>Added:
Table 2 Labs to Be Performed in the Event of a Platelet Count < 75,000/mm^3.
Note: The following labs may change as additional data is assessed, and sites will be updated regarding any changes.
<table>
<tr><th>To Be Performed at Local Lab</th></tr>
<tr><td>Peripheral smear (should be performed locally, fixed and sent to central lab for review)</td></tr>
<tr><td>Fibrinogen split products or D-dimer on fresh blood</td></tr>
<tr><th>To Be Performed at Central Lab</th></tr>
<tr><td>Citrated sample for platelets
Coagulation panel (PT/INR, aPTT)
CBC with reticulocytes</td></tr>
<tr><td>Fibrinogen</td></tr>
<tr><td>von Willebrand factor</td></tr>
<tr><td>Total globulins, total IgA, IgG and IgM</td></tr>
<tr><td>Complement: total C3, total C4, Bb, C5a</td></tr>
<tr><td>hsCRP</td></tr>
</table></td><td>To increase platelet count monitoring for safety purposes.</td></tr>
</table>

<table>
<tr><th>Protocol Section</th><th>Description of Change</th><th>Rationale</th></tr>
<tr><td>8.5.2 Safety Monitoring for Platelet Count Results Continued</td><td>
<table>
<tr><td>To Be Performed at Central Lab Continued</td></tr>
<tr><td>Serology for:</td></tr>
<tr><td>HBV, HCV, HIV (if not done recently for screening)</td></tr>
<tr><td>Rubella</td></tr>
<tr><td>CMV</td></tr>
<tr><td>EBV</td></tr>
<tr><td>Parvo B19</td></tr>
<tr><td>Helicobacter pylori (IgG serum test)</td></tr>
<tr><td>Auto-antibody screen:</td></tr>
<tr><td>Antiphospholipid</td></tr>
<tr><td>Rheumatoid factor</td></tr>
<tr><td>Anti-dsDNA</td></tr>
<tr><td>Anti-thyroid</td></tr>
<tr><td>To Be Performed at Specialty Lab(s)</td></tr>
<tr><td>Antiplatelet antibodies and Anti-PF4 assay</td></tr>
<tr><td>Anti-ASO antibody</td></tr>
</table>
</td><td>To increase platelet count monitoring for safety purposes.</td></tr>
<tr><td>Section 10.3 Populations</td><td>Updated:
Full Analysis Set (FAS): All patients who are enrolled and received at least 1 dose of active Study Drug and have a baseline TG assessment.
PK Population: All patients who are enrolled, receive at least 1 dose of volanesorsen, and have at least 1 post first dose PK sample collected, analyzed, and reported.</td><td>Modified to include, in the FAS, only those patients that are randomized and dosed and have a baseline TG assessment and clarified the PK Population.</td></tr>
<tr><td>Section 10.4 Definition of Baseline</td><td>Added:
For Group 3 patients, the baseline for fasting lipid measurements is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 in this open-label study, and the baseline for other assessments is defined as the last non-missing assessment prior to the first dose of Study Drug.</td><td>To add the baseline definition for Group 3 patients.</td></tr>
<tr><td>Appendix A: Schedule of Procedures
Appendix B: List of Laboratory Analytes</td><td>Added:
Troponin I at Screening (Group 3 patients only) and Weeks 13, 26, 52, and 65 (All abnormal troponin samples will be rerun at the central laboratory and also analyzed for CK-MB).
Platelet bound autoantibody testing at baseline (may be done).
Medical history, hepatitis B, C, and HIV at Screening (Group 3 patients only).</td><td>To ensure that Troponin I is monitored in patients that did not previously receive volanesorsen (i.e., Group 3 patients and placebo patients from the index studies) consistently with what was done in the ISIS 304801-CS6 index study.
To increase platelet count monitoring for safety purposes.
To make the eligibility criteria for the Group 3 patients consistent with those for the ISIS 304801-CS6 index study patients.</td></tr>
</table>

PROTOCOL SYNOPSIS

Protocol Title	An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Study Phase	3
Indication	Familial Chylomicronemia Syndrome
Study Objectives	To evaluate the safety and efficacy of dosing and extended dosing with volanesorsen (volanesorsen sodium 300 mg) in patients with FCS
Study Design	This is a multi-center open-label study of: Group 1: ISIS 304801-CS6 (index study) roll-over FCS patients Group 2: ISIS 304801-CS16 (index study) roll-over FCS patients Group 3: FCS patients who did not participate in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies All patients will receive volanesorsen 300 mg once per week for 52 weeks. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period. Following the Week 52 visit, patients will have the option of participating in an expanded access program or continuing dosing for up to an additional 52 weeks until an expanded access program is approved and available in their country. Patients not participating in an expanded access program will enter a 13-week post-treatment evaluation period
Number of Patients	Up to approximately 70 patients dosed
Study Population	Inclusion Criteria: 1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law 2. Age ≥ 18 years at time of informed consent 3. Groups 1 and 2: Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement. Groups 2 and 3: Patients must also meet the following criteria in order to enter into the open-label study: a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L) b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) by documentation of the following: • Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1) c. Group 2: Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 index study Group 3: Fasting TG ≥ 750 mg/dL at Screening for this open-label study 4. Able and willing to participate in a 65-week study

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	Inclusion Criteria: *Continued* 5. Satisfy 1 of the following: a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved), abstinent*, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration b. Males: Surgically sterile, abstinent* or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration * Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception Exclusion Criteria for Group 1 (ISIS 304801-CS6) and Group 2 (ISIS 304801-CS16) Index Study Roll-over Patients 1. Have any new condition or worsening of existing condition which in the opinion of the Investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study 2. Unwilling to comply with lifestyle requirements for the duration of the study (Section 6.3) Exclusion Criteria for Group 3 (patients who did not participate in an index study) 1. Diabetes mellitus with any of the following: a. Newly diagnosed within 12 weeks of screening b. HbA1c ≥ 9.0% at Screening c. Recent change in anti-diabetic pharmacotherapy (change in dosage or addition of new medication within 12 weeks of screening [with the exception of ± 10 units of insulin]) d. Anticipated need to change dose or type of medication during the treatment period of the Study (with the exception of ± 10 units of insulin) e. Current use of GLP-1 agonists 2. Severe hypertriglyceridemia other than due to familial chylomicronemia syndrome 3. Active pancreatitis within 4 weeks prior to screening

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	Exclusion Criteria for Group 3 (patients who did not participate in an index study) *Continued* 4. History within 6 months of screening of acute or unstable cardiac ischemia (myocardial infarction, acute coronary syndrome, new onset angina), stroke, transient ischemic attack or unstable congestive cardiac failure requiring a change in medication or major surgery within 3 months of screening 5. Any of the following laboratory values at Screening a. Hepatic: • Total bilirubin > upper limit of normal (ULN), unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL • ALT > 2.0 x ULN • AST > 2.0 x ULN b. Renal: • Persistently positive (2 out of 3 consecutive tests ≥ 1+) for protein on urine dipstick. In the event of a positive test eligibility may be confirmed by a quantitative total urine protein measurement of < 500 mg/24 hrs • Persistently positive (2 out of 3 consecutive tests ≥ trace positive) for blood on urine dipstick. In the event of a positive test eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field • Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault < 50 mL/min (MDRD or CKD-EPI formulas can be used instead of Cockcroft-Gault for estimation of GFR in patients with low body weight after discussion with Sponsor Medical Monitor) c. Cardiac Troponin I > ULN at Screening d. LDL-C > 130 mg/dL at Screening e. Any other laboratory abnormalities which, in the opinion of the Investigator or the Sponsor, would make the patient unsuitable for inclusion 6. Uncontrolled hypertension (BP > 160/100 mm Hg) 7. History of bleeding diathesis or coagulopathy or clinically-significant abnormality in coagulation parameters at Screening 8. History of heart failure with NYHA greater than Class II 9. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1 10. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B 11. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated 12. Treatment with another investigational drug, biological agent, or device within 1 month of screening, or 5 half-lives of investigational agent, whichever is longer

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	Exclusion Criteria for Group 3 (patients who did not participate in an index study) *Continued* 13. Unwilling to comply with lifestyle requirements (Section 6.3) 14. Use of any of the following: a. Statins, omega-3 fatty acids (prescription and OTC), or fibrates unless on a stable dose for at least 3 months prior to screening and dose and regimen expected to remain constant during the treatment period. Patients taking OTC omega-3 fatty acids should make every effort to remain on the same brand throughout the study b. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to screening c. Systemic corticosteroids or anabolic steroids within 6 weeks prior to screening unless approved by the Sponsor Medical Monitor d. Atypical antipsychotic medications (e.g., olanzapine and clozapine) unless on a stable dose for at least 3 months prior to screening and dose and regimen expected to remain stable throughout the study e. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to screening and dose and regimen expected to remain constant during the treatment period f. Glybera gene therapy within 2 years prior to screening g. Oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, and apixaban) unless on a stable dose for at least 4 weeks prior to screening and regular clinical monitoring is performed h. Tamoxifen, estrogens or progestins unless on a stable dose for at least 4 months prior to screening and dose and regimen expected to remain constant during the treatment period i. Plasma apheresis within 4 weeks prior to screening or planned during the study j. Prior exposure to ISIS 304801 k. Any other medication unless stable at least 4 weeks prior to screening (Occasional or intermittent use of over-the-counter medications will be allowed at Investigator's discretion) 15. Blood donation of 50 to 499 mL within 30 days of screening or of > 499 mL within 60 days of screening 16. Known hypersensitivity to any of the excipients of the Study Drug (ISIS 304801 or placebo) 17. Have any other conditions, which, in the opinion of the Investigator or the Sponsor would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the study
Treatment Group	Volanesorsen 300 mg once per week
Study Drug Administration	Volanesorsen will be administered as subcutaneous (SC) injections.
Dose Adjustments	Dose adjustments, including dose interruptions and/or decreasing the dose frequency will be allowed for safety or tolerability after consultation with the Sponsor Medical Monitor.

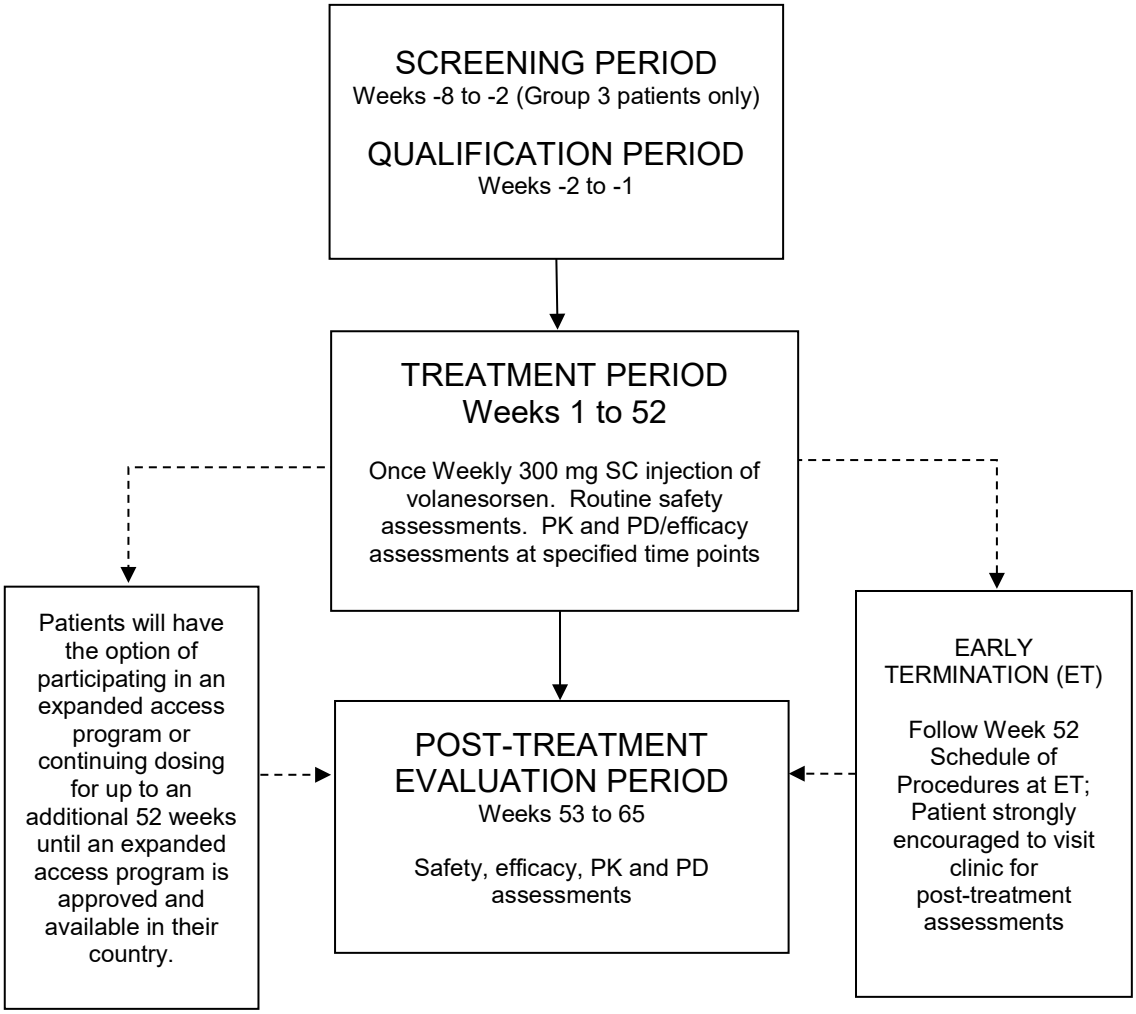
PROTOCOL SYNOPSIS *Continued*

Rationale for Dose and Schedule Selection	The dose of 300 mg once weekly was chosen for the double-blinded placebo-controlled Phase 3 index studies (ISIS 304801-CS6 and ISIS 304801-CS16) based on the pharmacodynamic and safety analysis of the Phase 2 studies (Section 2.4) which included a subset of patients with FCS. The same dose of 300 mg once weekly will be used in this open-label study of FCS patients.
Study Visit Schedule and Procedures	The study for an individual patient will generally consist of the following periods: • Group 1 and 2 patients (participated in ISIS 304801-CS6 or ISIS 304801-CS16 index study): A qualification period of up to 2 weeks (unless approved by the Sponsor). Please refer to Section 4.1 and Appendix A • Group 3 patients (did not participate in an index study): An up to 8-week screening and qualification period, including a diet stabilization period of at least 6 weeks (screening and diet stabilization period may be reduced, per Sponsor approval, if the patient is following a diet for optimal control of TGs and disease management prior to screening). Please refer to Section 6.1.2 and Appendix A • All patients: o A 52-week treatment period during which volanesorsen will be administered as a once weekly SC injection o Option to participate in an extended treatment period (up to an additional 52 weeks) o A 13-week post-treatment evaluation period or expanded access program The patients, Investigators, study staff, and the Sponsor will remain blinded to lipid data through the last patient's Week 13 visit of the open-label study or until results from the database locks for the ISIS 304801-CS6 and ISIS 304801-CS16 index studies becomes available, whichever comes first. Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), adverse events (AE), concomitant medication/procedure information, lipid panel, volanesorsen plasma concentrations, immunogenicity (IM) testing, liver/spleen magnetic resonance imaging (MRI), ECGs, echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Dietary counseling will be repeated at intervals throughout the treatment and follow-up period and a daily food/drink diary will be completed for the week prior to each quarterly visit by each patient. Following the Week 52 visit, patients will have the option of participating in an expanded access program or continuing dosing for up to an additional 52 weeks until an expanded access program is approved and available in their country. Patients not participating in an expanded access program will enter the 13-week post-treatment evaluation period.

PROTOCOL SYNOPSIS *Continued*

Safety and Tolerability Evaluations	Overall safety and tolerability of volanesorsen will be assessed by determining the incidence and severity of adverse and serious adverse events (including independently adjudicated events of acute pancreatitis and MACE), withdrawals due to adverse events, and changes in laboratory and other safety parameters.
Planned Analyses	Safety Endpoints: • Adverse events including adjudicated events of acute pancreatitis and MACE • Vital signs and weight • Physical examinations • Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis) • Echocardiography • Electrocardiograms (ECGs) • Use of concomitant medications • MRIs Efficacy Endpoints: • Percent change and absolute change from baseline in fasting TG • Frequency and severity of patient reported abdominal pain during the treatment period • Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-high-density lipoprotein-cholesterol (non-HDL-C), apolipoprotein B [apoB], high-density lipoprotein-cholesterol (HDL-C), apolipoprotein A-1 [apoA-1], very-low-density lipoprotein-cholesterol (VLDL-C), and LDL-C • Percent change from baseline in fasting total apolipoprotein C-III (apoC-III) • Quality of Life questionnaires (EQ-5D, SF-36) • Adjudicated acute pancreatitis event rate • Other symptoms: eruptive xanthoma, lipemia retinalis
Pharmacokinetic Evaluations	Plasma samples will be taken from all patients for the measurement of volanesorsen as follows: trough levels (pre-dose) throughout treatment and post-treatment levels during the post-treatment follow-up period. In a subset of patients, more frequent assessment of plasma concentrations of volanesorsen will be performed to determine volanesorsen pharmacokinetic parameters. Plasma sample collection time points are detailed in Appendix A and Appendix C.
Statistical Considerations	No sample size calculations were performed as this is an open-label study.
Sponsor	Ionis Pharmaceuticals, Inc.
Collaborator	Akcea Therapeutics

STUDY DESIGN AND TREATMENT SCHEMA



STUDY GLOSSARY

Abbreviation/Acronym	Definition
ADA	anti-drug antibody
AE	adverse Event
ALP	alkaline Phosphatase
ALT	alanine Aminotransferase
ANA	antinuclear Antibody
apoA-1	apolipoprotein A-1
apoB	apolipoprotein B
apoC-III	apolipoprotein C-III
apoE	apolipoprotein E
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
CBC	complete blood count
C_{max}	maximum observed drug concentration
CRF	case report form
DNA	deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
ET	early termination
FAS	full analysis set
FCS	Familial Chylomicronemia Syndrome
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
GPIHBP1	glycosylphosphatidylinositol-anchored hdl-binding protein 1
HAPI	heritability and phenotype intervention
HbA1c	glycated hemoglobin
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein-cholesterol
hsCRP	High-sensitivity C-reactive protein
ICH	International Conference on Harmonization
IDL	intermediate density lipoprotein
IEC	Independent Ethics Committee
IM	immunogenicity
Index Studies	ISIS 304801-CS6 and ISIS 304801-CS16

INR	International Normalized Ratio
IRB	Institutional Review Board
IXRS	Interactive Voice/Web-Response System
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein-cholesterol
LMF1	lipase maturation factor 1
LPL	lipoprotein lipase
MACE	major acute cardiovascular event
MOE	2′-*O*-(2-methoxyethyl)
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NCS	not clinically-significant
NOAEL	no-observed-adverse-effect level
non-HDL-C	non-high-density lipoprotein-cholesterol
OTC	over the counter
PFS	prefilled syringe
PD	pharmacodynamic
PK	pharmacokinetic
PPS	per protocol set
PT	prothrombin time
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SUSAR	suspected unexpected serious adverse reaction
T2DM	type 2 diabetes mellitus
T_{max}	time to maximal concentration
TG	triglycerides
Treatment-emergent	occurring after first dose of Study Drug
TRL	triglyceride-rich lipoproteins
ULN	upper limit of normal
VLDL	very-low-density lipoprotein
VLDL-C	very-low-density lipoprotein-cholesterol
VLDL-TG	lipoprotein-triglyceride
WMA	World Medical Association

1. OBJECTIVES

The objective of the study is to evaluate the safety and efficacy of dosing and extended dosing with volanesorsen in patients with familial chylomicronemia syndrome.

2. BACKGROUND AND RATIONALE

2.1 Overview of Disease

Familial Chylomicronemia Syndrome (FCS) is an inherited disease characterized by severe hypertriglyceridemia and chylomicronemia, and risk or history of pancreatitis. It is a rare autosomal recessive disease that can be diagnosed either in childhood or adulthood.

Fasting plasma triglyceride (TG) levels in FCS patients are typically 10-fold to 100-fold above normal (1,500 to 15,000 mg/dL), despite extreme dietary fat restriction (20 g or approximately 15-20% of daily calorie intake) (Brunzell 1999-2011). Patients with FCS often present in infancy or childhood with frequent and severe abdominal pain, repetitive colicky pain, repeated episodes of potentially fatal acute pancreatitis, and failure to thrive (Brunzell 1999-2011; Tremblay et al. 2011). Physical examination frequently reveals eruptive xanthomas, lipemia retinalis and hepatosplenomegaly, and plasma from patients appears lactescent, interfering with determination of other laboratory parameters (Tremblay et al. 2011).

Patients with fasting triglyceride levels > 10 mmol/L probably have a component of chylomicronemia. Clinical diagnosis would include evidence of clinical features of chylomicronemia syndrome and secondary causes such as uncontrolled type 1 or type 2 diabetes mellitus (T2DM), hypothyroidism, poor diet, alcohol use, nephrotic syndrome or use of associated medications should be ruled out. The diagnosis of FCS may be made more specifically by genotyping or confirmation of very low or absent lipoprotein lipase (LPL) enzyme activity in post heparin plasma (Brunzell 1999-2011).

Patients with FCS carry a heavy burden of medical complications, the most serious, as described above, being an extreme risk of recurrent and potentially fatal pancreatitis. Due to the recurrent episodes of acute pancreatitis, these patients may also develop chronic pancreatitis and signs of exocrine or endocrine pancreatic insufficiency, including diabetes mellitus (Gaudet et al. 2013). While the pathophysiology underlying chylomicron-related pancreatitis has not been completely elucidated, 1 hypothesis is that large chylomicrons lodged in pancreatic capillaries are exposed to pancreatic lipase, with the subsequent release of free fatty acids through the hydrolysis of chylomicron-associated TGs. High concentrations of free fatty acids are thought to damage pancreatic cells leading to emergent pancreatitis (Yang et al. 2009; Berglund et al. 2012).

The etiology of extreme hypertriglyceridemia in FCS is considered to be ineffective triglyceride clearance, due to an extremely low level of LPL activity. LPL normally functions to hydrolyze triglycerides (TG) in chylomicrons along the luminal surface of capillaries, mainly in heart, skeletal muscle, and adipose tissue, promoting triglyceride clearance from the circulation. LPL is regulated by a number of key genes, and loss-of-function mutations in one of these genes, or the LPL gene itself, results in FCS (Surendran et al. 2012). In addition to loss of function mutations, null mutations, and nonsense mutations in the LPL gene, other genes currently identified in FCS patients, and known to directly influence LPL activity include: apolipoprotein C-II (APOC2) a cofactor for LPL (Schuster et al. 2011); apolipoprotein A-V

(APOA5) an enhancer of LPL activity (Schaap et al. 2004); lipase maturation Factor 1 (LMF1), a transmembrane protein involved in LPL maturation (Doolittle et al. 2009); glycosylphosphatidylinositol-anchored HDL-binding protein 1 (GPIHBP1), a capillary endothelial cell protein that provides a platform for LPL-mediated processing of chylomicrons (Beigneux et al. 2007).

2.2 Therapeutic Rationale

Apolipoprotein C-III (ApoC-III), a key regulator of plasma triglyceride levels, is a 79 amino acid glycoprotein synthesized principally in the liver (Ooi et al. 2008; Figure 1). ApoC-III is a major regulator of lipoprotein metabolism and plays a pivotal role in regulating plasma TG levels (Chan et al. 2008). It is a component of triglyceride-rich lipoproteins (TRLs) and a potent inhibitor of LPL (Lemieux et al. 2003). At higher concentrations apoC-III also inhibits hepatic lipase activity (Kinnunen and Ehnolm 1976), an enzyme which plays an important role in the conversion of dense very-low-density lipoprotein (VLDL) to intermediate density lipoprotein (IDL) and to LDL (Mendivil et al. 2010), as well as in the remodeling of HDL (Brown et al. 2010). In addition, increased apoC-III content adversely affects apoE-mediated hepatic uptake of TG-rich remnants (Mann et al. 1997). Thus, elevated plasma apoC-III levels are associated with impaired hydrolysis and retarded clearance of TG-rich particles, resulting in the accumulation of lipoprotein-triglyceride (VLDL-TG) and chylomicrons in plasma and the development of hypertriglyceridemia (Ito et al. 1990).

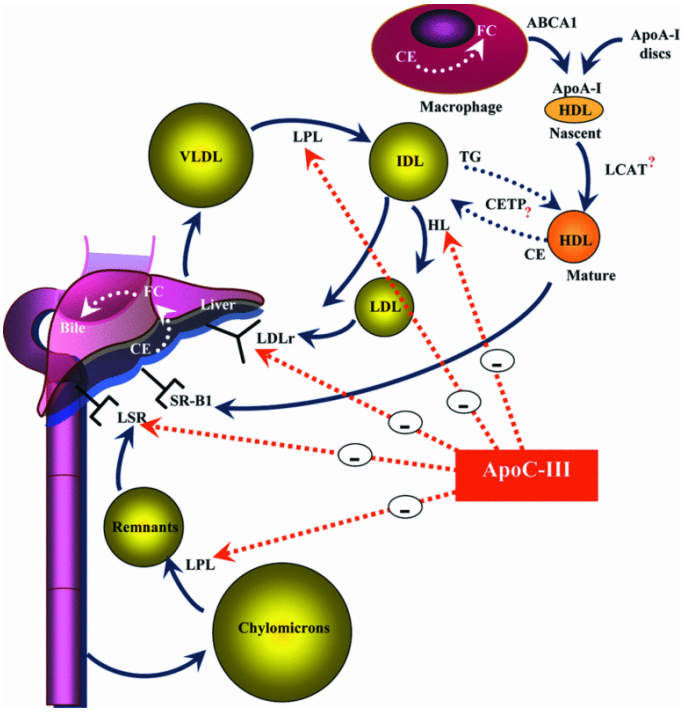


Figure 1 ApoC-III Regulates Lipoprotein Metabolism by Multiple Mechanisms

From Ooi et al. 2008; ABCA1 = ATP-binding cassette A1, apo = apolipoprotein, CE = cholesterol ester, CETP = cholesterol ester transfer protein, FC = free cholesterol, HDL = high-density lipoprotein, HL = hepatic lipase, IDL = intermediate-density lipoprotein, LCAT = lecithin cholesterol acyltransferase, LDL = low-density lipoprotein, LDLr = LDL receptor, LPL = lipoprotein lipase, LSR = lipolysis-stimulated receptor, SR-B1 = scavenger receptor B-1, TG = triglyceride, VLDL = very low-density lipoprotein.

Mechanistically, FCS is primarily a consequence of ineffective clearance of TRL. ApoC-III is a prominent component of TRL (e.g., VLDL and chylomicrons). In addition to its role in inhibiting LPL, apoC-III inhibits TRL remnant (TG-depleted remnant lipoprotein) uptake by hepatic lipoprotein receptors by steric inhibition of the interaction of apoE with these receptors.

Human genetic data have demonstrated positive phenotypic associations with loss (e.g., null or nonsense mutations) and negative effects with gain of function mutations (Atzmon et al. 2006; Pollin et al. 2008; Petersen et al. 2010). A novel nonsense mutation in the apoC-III gene was identified in the heritability and phenotype intervention (HAPI) heart study in Old Order Amish that results in lower plasma apoC-III and TG levels and lower LDL-C, increased HDL-C and reduced atherosclerosis (Pollin et al. 2008). In another study involving a group of 214 Ashkenazi Jews of advanced age (had passed or nearly reached 100 years of age), genotype analysis revealed a polymorphism in the apoC-III gene (APOC3-641CC genotype) with a clear pattern of age-dependent frequency that was associated with significantly lower levels of apoC-III protein, a favorable lipoprotein profile and increased longevity (Atzmon et al. 2006). In contrast to the Amish and Ashkenazi apoC-III polymorphisms associated with lower plasma TG, apoC-III polymorphisms associated with higher plasma TG have also been recently described (Petersen et al. 2010). In a cohort of lean (mean body mass index [BMI] = 24.7 ± 3.6 kg/m^2) Asian Indians, carriers of apoC-III variant alleles (C-482T, T-455C, or both) were noted to have significantly higher plasma apoC-III and TG levels, and decreased ability to clear postprandial plasma TG from the circulation. Taken together, the available data strongly support the development of a therapy that reduces plasma apoC-III levels in order to reduce the very high circulating triglyceride and chylomicron levels that are accompanied by increasing risk for acute pancreatitis.

Given the profound reductions in TGs observed with volanesorsen treatment in FCS patients who have no detectable LPL activity (See Section 2.3.4), and the mechanistic data available to date on apoC-III function, potential mechanisms that explain how apoC-III inhibition results in triglyceride reduction in FCS patients include: (1) enhancing the very small residual amounts of LPL activity that these patients may have, below the limit of detection of the assay in many cases (2) potentially enhanced activity of other lipases also involved in the metabolism and breakdown of TGs, such as hepatic lipase or endothelial lipase (Kinnunen and Ehnolm 1976), and (3) apoC-III interaction with Apolipoprotein E (apoE), an important factor in liver reuptake of lipid particles by blocking apoE-mediated uptake of lipid particles in the liver (Breyer et al. 1999), and therefore, reducing apoC-III might enhance apoE-mediated uptake of lipid particles. Volanesorsen-mediated reduction of apoC-III could be contributing to one or all of these mechanisms resulting in the observed potent and sustained reductions in TG.

Through a novel apoC-III lowering mechanism of action, volanesorsen may provide the potential to manage triglyceride levels in FCS patients.

2.3 Volanesorsen

2.3.1 Mechanism of Action

Volanesorsen is a second-generation antisense oligonucleotide (ASO) drug targeted to human apoC-III. It is complementary to a region within the 3′ untranslated region of the apoC-III messenger ribonucleic acid (mRNA) and binds to the mRNA by Watson and Crick base pairing.

The hybridization (binding) of volanesorsen to the cognate mRNA, results in the RNase H1-mediated degradation of the apoC-III mRNA, thus preventing production of the apoC-III protein. Maximal antisense-mediated reduction of target mRNA levels is typically greater than 90% of control levels in sensitive tissues (Crooke and Bennett 1996; Zhang et al. 2010). Furthermore, reduction in target mRNA levels using this approach correlates directly with a subsequent reduction in target protein levels.

2.3.2 Chemistry

Chemically, volanesorsen is a synthetic oligomer of 20 nucleotides (i.e., a 20-mer) that are connected sequentially by phosphorothioate linkages. The nucleotide sequence of volanesorsen (Figure 2) is complementary to a 20-nucleotide stretch within the 3′ untranslated region of the apoC-III mRNA transcript at base position 489-508. Structurally, the oligonucleotide has 3 regions. Two (2) of them, the 5 nucleotides at the 5′ end and the 5 nucleotides at the 3′ end, are composed of 2′-*O*-(2-methoxyethyl) (MOE)-modified ribonucleotides. These MOE-modified nucleotides confer (1) increased affinity to the target mRNA (Altmann et al. 1996; McKay et al. 1999), (2) increased resistance to exonucleases and endonucleases (thereby increasing stability in tissue) (Geary et al. 2003), and (3) amelioration of some of the high dose toxicities thereby resulting in an improved safety profile compared to first generation antisense drugs containing phosphorothioate modified oligodeoxynucleotides (DNA) (Henry et al. 2000). The third region, the central portion of the oligonucleotide, is composed of 10 oligodeoxynucleotides. This chimeric design is called a MOE-Gapmer, and volanesorsen employs this chimeric structure to enable use of the RNase H1-mechanism for antisense activity. This is because while the 2′-MOE modification confers increased stability and affinity, it does not support RNase H1 catalysis of RNA hybridized to 2′-MOE-modified nucleotides (McKay et al. 1999). This is caused by conformational changes induced in the heteroduplex by 2′-alkoxy:RNA hybrids that are not recognized by RNase H1 enzymes (Inoue et al. 1987; Monia et al. 1993). By limiting the 2′-MOE modification to nucleotides flanking the phosphorothioate oligodeoxynucleotide core, the beneficial attributes of the 2′-MOE chemistry are preserved while also retaining RNase H1 recognition.

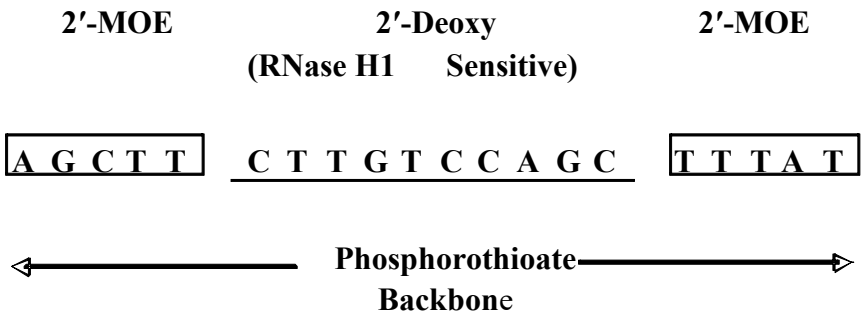


Figure 2 Design of Chimeric 2′-MOE Phosphorothioate Oligonucleotides (MOE-Gapmer). The sequence of volanesorsen is shown

2.3.3 Preclinical Experience

Inhibition of apoC-III using volanesorsen has been shown to potently reduce hepatic apoC-III mRNA as well as plasma apoC-III protein and TG in a dose- and time-dependent fashion in several species, including human apoC-III transgenic mice, and other rodent and monkey models. Treatment with volanesorsen also resulted in reduced VLDL and chylomicron TG and reduced postprandial TG in hypertriglyceridemic monkeys (Graham et al. 2013).

The pharmacokinetics (PK) and toxicity of volanesorsen have been assessed in mice, rats, and cynomolgus monkeys. General toxicity studies with volanesorsen for up to 39 weeks of treatment followed by up to a 20-week recovery period are complete. The preclinical toxicology program for volanesorsen consists of single dose safety pharmacology studies in the monkey (cardiovascular) and mouse (neurobehavioral and pulmonary assessment studies), *in vitro* and *in vivo* genetic toxicity assessment, repeat dose fertility and/or developmental reproductive toxicology studies in the mouse and rabbit and evaluation in the *in vitro* human Ether-á-go-go-related gene (hERG) assay.

Volanesorsen treatment-related findings in mice and monkeys were generally consistent with those expected for the 2′-MOE-class of ASOs. Treatment-related findings included effects consistent with drug accumulation in tissues in rodents and monkeys, species-dependent proinflammatory response in rodents and monkeys and complement activation and reductions in platelet counts in the monkey. In the mouse and monkey general toxicity studies, reduction of hepatic apoC-III mRNA (> 75%) was not associated with any findings that could be considered related to the pharmacologic inhibition of apoC-III for up to 39 weeks of treatment.

The long-term, chronic toxicology studies in rodents with volanesorsen produced a significant proinflammatory response that led to subsequent effects on the heart at high doses. The rodent species are most sensitive to the proinflammatory effects of antisense molecules. Importantly, these effects on the heart were not observed in the monkey chronic toxicity studies even at the highest doses tested where drug exposure was higher than that in rodents.

Because these changes were not observed in monkeys, the findings in the heart are considered to be rodent-specific and not relevant to humans. Nevertheless, such effects will be monitored by measurement of echocardiograms that will be included in this clinical study.

Volanesorsen caused no untoward effects in safety pharmacology studies (*in vitro* and *in vivo*) and was non-genotoxic (*in vitro* and *in vivo*). Volanesorsen had no effects on fertility or embryo/fetal development in the mouse or rabbit reproductive toxicity studies. In these studies, volanesorsen was detected in placental tissue but not in fetal tissue indicating that little, if any, drug was able to cross the placenta to reach the fetus. Reduction of apoC-III mRNA (64% in males and 47% in females) also did not affect fertility or cause untoward effects on embryo/fetal development in mice.

Detailed information concerning the preclinical studies conducted with volanesorsen can be found in the volanesorsen Investigator's Brochure.

2.3.4 Clinical Experience

Detailed information concerning the clinical studies conducted with volanesorsen can be found in the volanesorsen Investigator's Brochure. A summary is included below.

Volanesorsen has been evaluated in one Phase 1 study and two Phase 2 studies, all double blinded and placebo controlled. The total exposures comprise 99 patients and healthy volunteers administered volanesorsen from 50 to 400 mg subcutaneously up to 3 months (compared to 37 administered placebo).

All clinical trials of volanesorsen have shown large and clinically meaningful reductions in fasting plasma apoC-III and TG (~80% and 70%, respectively, mean reduction from baseline with 300 mg dose) with a very high degree of consistency of response between the different patient groups. This includes healthy volunteers, patients with moderate to severe hypertriglyceridemia not on background TG-lowering therapy, patients with moderate to severe hypertriglyceridemia on a background stable fibrate therapy (Gaudet et al. 2015), patients with FCS, and patients with T2DM.

In a Phase 2 study, 3 patients with FCS were treated with 300 mg/wk volanesorsen in an open-label fashion. These patients had a mean baseline fasting TG level of 1,844 mg/dL and all 3 patients achieved TG levels below or close to 500 mg/dL during the dosing period out to Day 92 (Figure 3). Two (2) of the FCS patients had an absolute reduction in fasting TG in excess of 1,500 mg/dL (Gaudet et al. 2014).

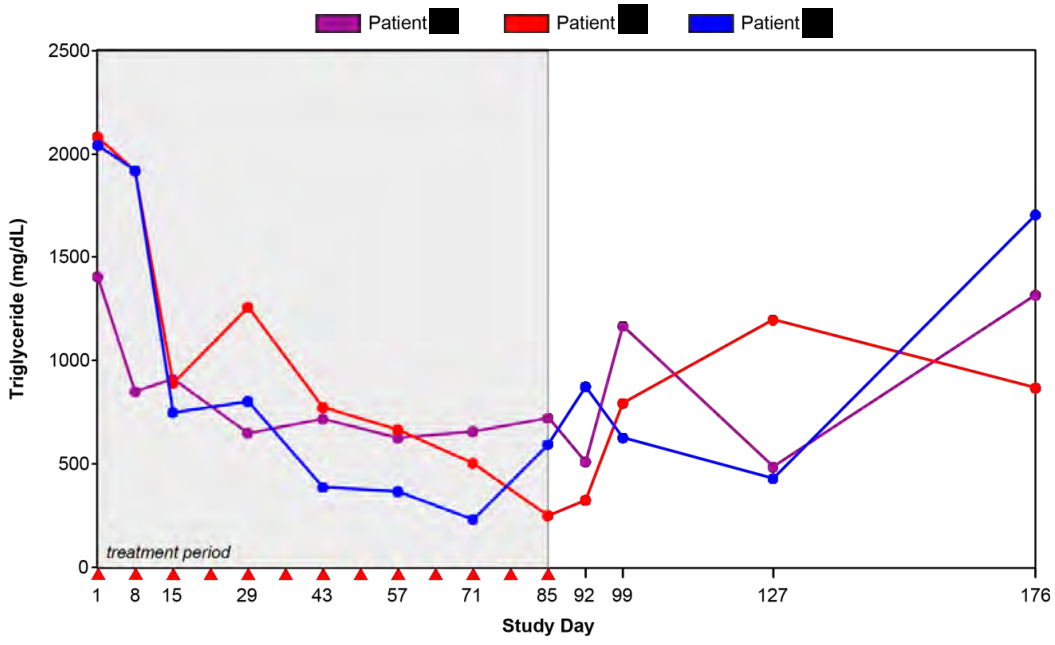


Figure 3 Fasting Triglycerides in Patients with FCS Treated with Volanesorsen

In clinical studies conducted to date volanesorsen has been well-tolerated and has shown a favorable safety profile. There has been no clinical or laboratory evidence of drug-drug interactions.

In the completed studies there have been no volanesorsen associated laboratory abnormalities suggestive of an effect on the renal (serum creatinine, proteinuria) or hepatic systems (alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin). In Phase 2 studies, there was a mild decrease of platelet count associated with volanesorsen administration that recovered in the post-treatment period and was not associated with platelet-related adverse events (AEs). In the blinded ongoing clinical trials of ISIS 304801, 2 patients of 142 dosed (as of February 29, 2016) had a decrease in platelet count to less than 50,000/mm^3 in the absence of major bleeding or clinically-relevant non-major bleeding and had Study Drug paused as per the monitoring and stopping rules for platelet counts (Section 8.6.3). Platelet counts recovered following suspension of dosing.

The most frequently observed AEs with volanesorsen were local reactions at the injection site. Local cutaneous reactions at the injection site defined as those events presenting as either pain, tenderness, erythema, pruritus or swelling occurring on the day of injection and persisting for at least 2 days were infrequent (~15% of injections), were almost always mild, resolved spontaneously, were non-progressive, and were not associated with systemic sequelae.

2.4 Rationale for Dose and Schedule of Administration

The dose and schedule selected for this study is 300 mg per week for 52 weeks. The dose of 300 mg per week is supported by both the cumulative nonclinical data available to date and the Phase 2 clinical data. In nonclinical studies, volanesorsen treatment-related effects in rodents and monkeys were consistent with drug accumulation in tissues and also include species-specific proinflammatory responses. In the monkey, the No-Observed-Adverse-Effect Level (NOAEL) was defined by the cumulative clinical pathology results and histopathology data which provide an adequate clinical margin. No nonclinical findings were considered to be related to the pharmacologic inhibition of apoC-III.

The safety data to date suggest that volanesorsen has been well-tolerated at dose levels up to 300 mg in patients with high triglycerides (including type 2 diabetes patients and administration in combination with fibrates and statins) with the most common AEs being local to the injection site and predominantly mild. A pooled analysis of safety for the Phase 2 studies did not demonstrate any clear difference in safety or tolerability between the different doses tested (100 mg, 200 mg, and 300 mg per week for 13 weeks).

Analysis of the cohorts in which volanesorsen was studied at different doses demonstrates dose-dependent pharmacology with respect to pharmacodynamic (PD) effect on the target, apoC-III, with a clear difference in the TG-lowering effect between the different doses in the 100 mg to 300 mg dose range as compared to placebo.

In addition to the nonclinical and clinical experience of volanesorsen, the dose and schedule of administration is supported by the preclinical and clinical safety experience of several other 2′-MOE-modified ASOs that have been safely administered intravenously and subcutaneously in multiple clinical studies at doses up to 1000 mg and for treatment durations that exceed 24 months (Santos et al. 2015).

3. EXPERIMENTAL PLAN

3.1 Study Design

This is an open-label study of:

Group 1: ISIS 304801-CS6 (index study) roll-over FCS patients

Group 2: ISIS 304801-CS16 (index study) roll-over FCS patients

Group 3: FCS patients who did not participate in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies

Up to approximately 70 patients will receive 300 mg once weekly volanesorsen for 52 weeks.

Following the Week 52 visit, patients will have the option of participating in an expanded access program or continuing dosing for up to an additional 52 weeks until an expanded access program is approved and available in their country. Patients not participating in an expanded access program will enter a 13-week post-treatment evaluation period.

3.2 Number of Study Centers

This study will be conducted at multiple centers worldwide.

3.3 Number of Patients

Up to approximately 70 patients will be dosed.

3.4 Overall Study Duration and Follow-up

The Study will consist of the following periods:

3.4.1 Group 1 and 2 Patients (participated in ISIS 304801-CS6 or ISIS 304801–CS16 index study): Qualification

A period of up to 2 weeks (unless approved by the Sponsor) is given to complete qualification assessments outlined in the Schedule of Procedures. Please refer to Section 4.1 and Appendix A.

3.4.2 Group 3 Patients (did not participate in an index study): Screening/Qualification

An up to 8-week screening and qualification period, including a diet stabilization period of at least 6 weeks (screening and diet stabilization period may be reduced, per Sponsor approval, if the patient is following a diet for optimal control of TGs and disease management prior to screening. Please refer to Section 6.1.2 and Appendix A.

3.4.3 Treatment

The treatment period is 52 weeks. Eligible patients will report to the Study Center for assessments at specified intervals throughout the 52-week treatment period as detailed in the Schedule of Procedures (Appendix A). During the treatment period, volanesorsen is administered by SC injection once weekly.

3.4.4 Post-Treatment

The post-treatment evaluation period is 13 weeks and consists of 4 Study Center visits on Weeks 54, 56, 58, and 65 (Weeks 54, 56, and 58 may be conducted by a home healthcare nurse).

3.5 End-of-Study

The End-of-Study is last patient, last visit.

3.6 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will review (as needed) safety, tolerability and efficacy data collected on volanesorsen during this study. Based on its ongoing assessment of the safety and tolerability of volanesorsen, the DSMB will provide recommendations to the Sponsor for modifying, stopping or continuing the study as planned. Details on the safety assessments, frequency of review and meeting schedules are outlined in the DSMB Charter and/or the statistical analysis plan (SAP).

4. PATIENT ENROLLMENT

4.1 Screening/Qualification

Before patients may be enrolled into the study, the Sponsor requires a copy of the Study Center's written independent ethics committee/institutional review board (IEC/IRB) approval of the protocol, informed consent form, and all other patient information.

Patients or their legally acceptable representatives must sign the consent form before any study-specific procedures or evaluations related to this open-label study are performed.

Groups 1 and 2 (Qualification): During the qualification period, the eligibility of the patient to enroll in the open-label study will be determined. Final assessments from the ISIS 304801-CS6 or ISIS 304801-CS16 studies may be used for qualification. A period of up to 2 weeks after completion of the ISIS 304801-CS6 or ISIS 304801-CS16 index studies (unless approved by the Sponsor) is given to complete qualification. Qualified patients will retain the unique patient identification number that was assigned to them during the ISIS 304801-CS6 or ISIS 304801-CS16 index studies. The patient identification number will be used to identify the patient throughout the extension trial and must be used on all study documentation related to that patient. The patient identification number must remain constant throughout the extension trial.

Group 3 (Screening and Qualification): At the time of consent, the patient will be considered enrolled into the study and will be assigned a unique screening number before any study procedures, including screening procedures, are performed. At the time of enrollment, patients will be assigned a unique patient identification number. This number will be used to identify the patient throughout the trial and must be used on all study documentation related to that patient. The screening number and patient identification number must remain constant throughout the entire trial. In the event the patient is re-consented and re-screened the patient must be given a new screening number. Screening numbers and patient identification numbers, once assigned, will not be re-used.

4.2 Enrollment

Patients will be enrolled into the treatment phase of the study after all Screening (Group3) and qualification assessments have been completed and after the Investigator has verified that they are eligible per criteria in Sections 5.1 and 5.2. No patient may begin treatment prior to enrollment.

Eligible patients will be enrolled using an Interactive Voice/Web-Response System (IXRS).

5. PATIENT ELIGIBILITY

To be eligible to participate in this study candidates must meet the following eligibility criteria within 2 weeks of Study Day 1, or at the time point specified in the individual eligibility criterion listed.

5.1 Inclusion Criteria

1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law
2. Age ≥ 18 years at time of informed consent
3. Groups 1 and 2: Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement.

   Groups 2 and 3: Patients must also meet the following criteria in order to enter into the open-label Study:

   a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L)

   b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) by documentation of the following:

      - Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1)

   c. Group 2: Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 index study

      Group 3: Fasting TG ≥ 750 mg/dL at Screening for this open-label study
4. Able and willing to participate in a 65-week study
5. Satisfy 1 of the following:

   a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory

involved), abstinent*, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration.

b. Males: Surgically sterile, abstinent* or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration.

* Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception

5.2 Exclusion Criteria for Group 1 (ISIS 304801-CS6) and Group 2 (ISIS 304801-CS16) Index Study Roll-over Patients

1. Have any new condition or worsening of existing condition which in the opinion of the Investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study.
2. Unwilling to comply with lifestyle requirements for the duration of the study (Section 6.3).

Exclusion Criteria for Group 3 (patients who did not participate in an index study)

1. Diabetes mellitus with any of the following:
   a. Newly diagnosed within 12 weeks of screening
   b. HbA1c $\geq$ 9.0% at Screening
   c. Recent change in anti-diabetic pharmacotherapy (change in dosage or addition of new medication within 12 weeks of screening [with the exception of $\pm$ 10 units of insulin])
   d. Anticipated need to change dose or type of medication during the treatment period of the Study (with the exception of $\pm$ 10 units of insulin)
   e. Current use of GLP-1 agonists
2. Severe hypertriglyceridemia other than due to familial chylomicronemia syndrome
3. Active pancreatitis within 4 weeks prior to screening
4. History within 6 months of screening of acute or unstable cardiac ischemia (myocardial infarction, acute coronary syndrome, new onset angina), stroke, transient ischemic attack or unstable congestive cardiac failure requiring a change in medication or major surgery within 3 months of screening
5. Any of the following laboratory values at Screening
   a. Hepatic:

- Total bilirubin > upper limit of normal (ULN), unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL
- ALT > 2.0 x ULN
- AST > 2.0 x ULN

b. Renal:

- Persistently positive (2 out of 3 consecutive tests ≥ 1+) for protein on urine dipstick. In the event of a positive test eligibility may be confirmed by a quantitative total urine protein measurement of < 500 mg/24 hrs
- Persistently positive (2 out of 3 consecutive tests ≥ trace positive) for blood on urine dipstick. In the event of a positive test eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field
- Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault < 50 mL/min (MDRD or CKD-EPI formulas can be used instead of Cockcroft-Gault for estimation of GFR in patients with low body weight after discussion with Sponsor Medical Monitor)

c. Cardiac Troponin I > ULN at Screening

d. LDL-C > 130 mg/dL at Screening

e. Any other laboratory abnormalities which, in the opinion of the Investigator or the Sponsor, would make the patient unsuitable for inclusion

6. Uncontrolled hypertension (BP > 160/100 mm Hg)
7. History of bleeding diathesis or coagulopathy or clinically-significant abnormality in coagulation parameters at Screening
8. History of heart failure with NYHA greater than Class II
9. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1
10. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B
11. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated
12. Treatment with another investigational drug, biological agent, or device within 1-month of screening, or 5 half-lives of investigational agent, whichever is longer
13. Unwilling to comply with lifestyle requirements (Section 6.3)

14. Use of any of the following:
    a. Statins, omega-3 fatty acids (prescription and OTC), or fibrates unless on a stable dose for at least 3 months prior to screening and dose and regimen expected to remain constant during the treatment period. Patients taking OTC omega-3 fatty acids should make every effort to remain on the same brand throughout the study
    b. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to screening
    c. Systemic corticosteroids or anabolic steroids within 6 weeks prior to screening unless approved by the Sponsor Medical Monitor
    d. Atypical antipsychotic medications (e.g., olanzapine and clozapine) unless on a stable dose for at least 3 months prior to screening and dose and regimen expected to remain stable throughout the study
    e. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to screening and dose and regimen expected to remain constant during the treatment period
    f. Glybera gene therapy within 2 years prior to screening
    g. Oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, and apixaban) unless on a stable dose for at least 4 weeks prior to screening and regular clinical monitoring is performed
    h. Tamoxifen, estrogens or progestins unless on a stable dose for at least 4 months prior to screening and dose and regimen expected to remain constant during the treatment period
    i. Plasma apheresis within 4 weeks prior to screening or planned during the study
    j. Prior exposure to ISIS 304801
    k. Any other medication unless stable at least 4 weeks prior to screening (Occasional or intermittent use of over-the-counter medications will be allowed at Investigator's discretion)
15. Blood donation of 50 to 499 mL within 30 days of screening or of > 499 mL within 60 days of screening
16. Known hypersensitivity to any of the excipients of the Study Drug (ISIS 304801 or placebo)
17. Have any other conditions, which, in the opinion of the Investigator or the Sponsor would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the study

6. STUDY PROCEDURES

6.1 Study Schedule

All required study procedures are outlined in Appendices A, B, C, and D.

6.1.1 Qualification (Groups 1 and 2)

Please refer to Section 4.1 and Appendix A.

6.1.2 Screening and Qualification (Group 3)

Before any study-specific procedures or evaluations are initiated, patients must sign and date the informed consent form. An 8-week period, including a diet stabilization period of at least 6 weeks (screening and diet stabilization period may be reduced, per Sponsor approval, if the patient is following a diet for optimal control of TGs and disease management prior to screening) is given to perform the screening evaluations. The qualification assessments will be performed at Week -2 to -1, ideally after patient eligibility has been determined, and on Study Day 1. Abnormal screening results may be retested for review by the Study Medical Monitor for eligibility purposes

6.1.3 Treatment Period

The patients, Investigators, study staff, and the Sponsor will remain blinded to lipid data through the last patient's Week 13 visit of the open-label study or until results from the database locks for the ISIS 304801-CS6 and ISIS 304801-CS16 index studies become available, whichever comes first.

During the treatment period, patients will report to the study center for clinic visits a minimum of 5 times during Weeks 1-52 (see Schedule of Procedures in Appendix A). Study Drug will be administered once weekly unless the patient is on a biweekly dosing schedule for safety reasons (Section 8.1). Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), AEs, concomitant medication/procedure information, lipid panel, volanesorsen plasma concentrations, immunogenicity (IM) testing, liver/spleen MRI, ECGs, echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Adverse events at the injection site should be collected as adverse events. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period and all patients will complete a daily food diary for one week prior to their quarterly visit. All blood and urine samples should be collected prior to volanesorsen administration. Blood sampling at Weeks 2.5, 4, 6, 8, 10, 12, 15, 17, 19, 21, 23, 25, 28, 30, 32, 34, 36, 40, 42, 44, 46, 48, and 50 may be conducted by a home healthcare nurse. Approval for study procedures to be conducted by a home healthcare nurse on other outpatient visit days will require prior approval by the Sponsor. Patients must be fasted prior to drawing all blood samples and samples drawn locally should also be sent to the central laboratory for analysis whenever possible. Every effort should be made to ensure the previous week's dose is given 7 days prior to a scheduled clinic visit. Dosing instructions and training will be provided to the patient where applicable.

All reasonable attempts should be made to ensure compliance with the visit schedule as outlined in Appendix A. However, in the event that a visit does not occur or is delayed, all subsequent visits should be calculated based on the time elapsed since Day 1 rather than from the date of the previous visit.

6.1.4 Extended Treatment Period

Patients will have the option of continuing dosing for up to an additional 52 weeks until an expanded access program is approved and available in their country.

During the extended treatment period, patients will report to the study center for clinic visits during Weeks 54-104 (see Schedule of Procedures in Appendix A). Study Drug will be administered once weekly unless the patient is on a biweekly dosing schedule for safety reasons (Section 8.1). Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), AEs, concomitant medication/procedure information, lipid panel, volanesorsen plasma concentrations, IM testing, ECGs, and physical examinations will be performed according to the Schedule of Procedures in Appendix A. Adverse events at the injection site should be collected as adverse events. Dietary counseling will be reinforced at intervals throughout the extended treatment period. All blood and urine samples should be collected prior to volanesorsen administration. Blood sampling at Weeks 54, 56, 58, 60, 62, 66, 68, 70, 72, 74, 78, 80, 82, 84, 86, 88, 92, 94, 96, 98, 100, and 102 may be conducted by a home healthcare nurse. Approval for study procedures to be conducted by a home healthcare nurse on other outpatient visit days will require prior approval by the Sponsor. Patients must be fasted prior to drawing all blood samples and samples drawn locally should also be sent to the central laboratory for analysis whenever possible. Every effort should be made to ensure the previous week's dose is given 7 days prior to a scheduled clinic visit. Dosing instructions and training will be provided to the patient where applicable.

6.1.5 Pharmacokinetic (PK) Subgroup

A subgroup of patients will participate in an extended PK collection. Patients in this subgroup will have more frequent PK sampling over a 24-hour period following the first dose on Study Day 1 in order to evaluate the plasma PK parameters of volanesorsen. Patients in this subgroup will have an additional visit to the clinic, or by a home healthcare nurse, on Day 2 to collect a 24-hour post-dose blood draw after dosing on Day 1. The detailed PK sampling schedules are outlined in Appendix C.

Participation in the PK subgroup is optional for sites and patients, and consent may be withdrawn for the subgroup-specific procedures (e.g., multiple blood draws for PK) without being withdrawn from the study. If a patient withdraws consent from the subgroup procedures, he/she should remain on study and continue to follow all the non-subgroup assessments and procedures as outlined in Appendix A.

6.1.6 Post-Treatment Period

After completion of the Week 52 visit assessments, patients will have the option of participating in an expanded access program or continuing dosing for up to an additional 52 weeks until an expanded access program is approved and available in their country as described in Section 6.1.4. Patients not participating in an expanded access program will enter the 13-week post-treatment evaluation period. This 13-week post-treatment evaluation period consists of 4 Study Center visits on Weeks 54, 56, and 58 (which may be conducted by a home healthcare nurse), and Week 65 as outlined in the Schedule of Procedures in Appendix A. Patients who complete, or terminate early from, the extended treatment period without subsequently participating in an expanded access program will enter a 13-week post-treatment evaluation

period consisting of 4 Study Center visits on Weeks 106, 108, and 110 (which may be conducted by a home healthcare nurse), and Week 117 as outlined in the Schedule of Procedures in Appendix A.

6.2 Additional Study Assessments

6.2.1 Laboratory Assessments

Laboratory analyte samples will be collected throughout the study. A list of these analytes is contained in Appendix B.

Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1-week and determined not to have met a stopping rule before dosing can continue.

If there is no reportable platelet count within 14 days of the last platelet count, the Investigator will contact the patient to hold dosing until a new platelet count is obtained and reviewed.

All platelet count results will be promptly reviewed by the Investigator to ensure that the count has not met the stopping rule and to determine whether the rate of decline is suggestive that the patient could be approaching the dose pause rule of 75,000/mm^3.

Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor.

6.2.2 Physical Exams and Vital Signs

Physical exams and vital signs will be performed as indicated in the Schedule of Procedures (Appendix A). Vital signs should include weight, blood pressure, pulse rate, respiratory rate and body temperature. Blood pressure and pulse rate will be recorded after the patient has been in a sitting position for at least 5 minutes. Semi-supine systolic and diastolic blood pressure should always be measured on the same arm (preferentially on the left arm). Height will be measured at the Day 1 visit.

6.2.2.1 Eruptive Xanthoma

At each visit, patients will be asked whether they have had any episodes of eruptive xanthoma since their last visit and the number/duration of the events will be recorded. Physical exams should also include skin examination for presence/resolution of eruptive xanthomas. If a patient experiences an episode of eruptive xanthoma during the study, photos of the area should be taken, if possible.

6.2.2.2 Lipemia Retinalis

If possible, lipemia retinalis will be assessed by fundus photography prior to administration of the first dose of Study Drug (for ISIS 304801-CS16 roll-over patients) and repeated at Week 52. Images will be evaluated by an independent assessor, blinded to the patient's treatment assignment.

6.2.3 Echocardiography

Echocardiography for assessment of left and right ventricular function and mitral and aortic valve function will be conducted at Week 26 and Week 52 in all patients. For the purpose of assessment of treatment-emergent changes, all echocardiograms will be evaluated on an ongoing basis by an independent central reader. Results will be provided to the DSMB for their review.

6.2.4 ECG

The ECG will be recorded after the patient has been resting in a supine position for at least 5 minutes. ECGs will be performed in triplicate at Week 13, Week 26, Week 38, Week 52, and Week 65. Patients in the Extended Treatment Period will have ECGs performed in triplicate at Week 76 and Week 104.

6.2.5 MRI

MRI of the liver and spleen will be conducted at Week 52 for all patients for whom MRI is not contraindicated, e.g., patients having metal implants.

MRIs will be conducted using standardized procedures and settings. MRIs will be read by an independent central reader to assess liver fat and liver and spleen size**.**

6.2.6 Quality of Life Assessments

All patients will complete Quality of Life Questionnaires (EQ-5D and SF-36) at Week 1, Week 13, Week 26, Week 52, and Week 65.

6.2.7 Disease Symptom Diary

All patients will complete a symptom questionnaire once a week starting at the beginning of the qualification period and continuing to the end of the post-treatment follow-up period (Week 65).

6.2.8 Diet Monitoring

The diets of patients enrolled in the study will be monitored as follows:

1. All patients will be required to maintain a 7-day food diary prior to Week 1, Week 13, Week 26, Week 52, and Week 65.

2. Patients will receive diet/alcohol counseling by qualified study personnel at clinic visits throughout the course of the study. Qualified study personnel will telephone the patient to provide diet/alcohol counseling for visits that are conducted by a clinical service. Patients in the Extended Treatment Period will receive diet/alcohol counseling by qualified study personnel at clinic visits only.

3. In addition to the 7-day food diary and the diet /alcohol counseling during clinic visits, telephone calls from a dietitian or qualified study personnel to assess as to how each patient is maintaining their diet may be conducted randomly during the treatment and post treatment follow-up periods.

6.2.9 Family History

Family history of hypertriglyceridemia and pancreatitis will be collected for each patient.

6.2.10 Chart Review for Incidents of Acute Pancreatitis in Medical History (Group 3)

Patient records will be reviewed for incidents of acute pancreatitis occurring up to 5 years prior to screening and information relating to these events will be collected for independent adjudication.

6.3 Restriction on the Lifestyle of Patients

6.3.1 Contraception Requirements

All male patients and women of childbearing potential must refrain from sperm/egg donation and either be abstinent† or, if engaged in sexual relations of child-bearing potential, practice effective contraception from the time of signing the informed consent form until at least 13 weeks after their last dose of study treatment.

Male patients must also encourage their female partner to use effective contraception from the time of signing the informed consent until 13 weeks after the subject's last dose of study treatment.

For the purposes of this Study, women of childbearing potential are defined as any female who has experienced menarche, and who does not meet 1 of the following conditions:

- Postmenopausal: 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved
- 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Post hysterectomy

For the purposes of the study, effective contraception is defined as follows:

For male patients:

- Effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the use of condoms together with spermicidal foam/gel/film/ cream/suppository. Male patients must also encourage their female partner to use effective contraception from the time of signing the informed consent until 3 months after the patient's last dose of study treatment. Effective contraceptive for the female partner includes: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or barrier methods (female condom*, diaphragm, sponge, cervical cap) together with spermicidal foam/gel/film/cream/suppository. Male patients with partners that are pregnant must use condoms to ensure that the fetus is not exposed to the Study Drug.

For female patients:

- Using 1 or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or any 2 barrier methods (a combination of male or female

condom* with diaphragm, sponge, or cervical cap) together with spermicidal foam/gel/film/cream/suppository.

* Note: A female condom and a male condom should not be used together as friction between the two can result in either product failing.

† Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception

6.3.2 Other Requirements

All patients will be required to fast for at least 10 hours and preferably not more than 12 hours before visits requiring fasted blood sampling.

All patients will be encouraged to follow a diet comprising ≤ 20 g fat per day during the study.

Alcohol should not be consumed during the study.

All patients will be given an instruction card that must be presented to the treating physician if a suspected case of pancreatitis occurs. The card will explain that the patient is in a clinical trial and that serum lipase and/or amylase measures should be done in order to adjudicate the event, based on Atlanta Classification (Banks et al. 2013). If serum or amylase activity is less than 3 x upper limit of normal (ULN), imaging, preferably contrast-enhanced computed tomography, should be considered to confirm the diagnosis of acute pancreatitis per the Atlanta Criteria.

7. STUDY DRUG

7.1 Volanesorsen Description

Volanesorsen drug product (ISIS 304801) characteristics are listed in Table 1.

Volanesorsen (ISIS 304801) is contained in glass prefilled syringes (PFS). Volanesorsen and its storage and preparation instructions will be provided by the Sponsor or designee. Volanesorsen must be stored securely at 2 to 8 °C and be protected from light.

Table 1 Volanesorsen (ISIS 304801) Characteristics

Strength	200 mg/mL
Volume/Formulation	1.5 mL solution per PFS
Dose	300 mg once weekly
Route of Administration	SC

7.2 Packaging and Labeling

The Sponsor will provide the Investigator with packaged volanesorsen labeled (ISIS 304801) in accordance with specific country regulatory requirements.

7.3 Study Drug Accountability

The study staff is required to document the receipt, dispensing, and return/destruction of volanesorsen provided by the Sponsor. The Study Center must return all unused volanesorsen to the Sponsor or designee. All used syringes must be disposed of as per the site's hazardous waste destruction policy.

8. TREATMENT OF PATIENTS

8.1 Volanesorsen Administration

For each individual patient, volanesorsen will be administered subcutaneously as a single 1.5 mL 300 mg injection once weekly for Weeks 1-52. Patients entering this ISIS 304801-CS7 study on a reduced dose or dose frequency of Study Drug (volanesorsen), for safety or tolerability reasons in their index study (ISIS 304801-CS6 or ISIS 304801-CS16), will receive a reduced dose or dose frequency of volanesorsen for continued safety or tolerability as outlined in Sections 8.5 and 8.6. Patients entering this CS7 study having dose or dose frequency reduced in the CS16 index study after 13 weeks of treatment, as outlined in CS16 Amendment 4 Section 8.7, can receive the 300 mg once weekly dose of volanesorsen.

Patients should receive 1 dose per week, with weeks always defined relative to Study Day 1. For example if a patient receives the first dose on a Monday, subsequent doses should be given on Mondays, if possible. If a patient misses an injection, or if dosing on the usual day is not possible, the patient can reschedule the injection provided that 2 doses are administered at least 2 days apart.

Every effort should be made to ensure the previous week's dose is given 7 days prior to a scheduled clinic visit.

Please refer to the Study Drug Manual provided by the Sponsor for more detailed instructions for volanesorsen preparation and administration.

8.2 Other Protocol-Required Drugs

There are no other protocol-required drugs (Section 6.2.5).

8.3 Other Protocol-Required Treatment Procedures

There are no other protocol required treatment procedures for this study.

8.4 Treatment Precautions

There are no specific treatment precautions required for this study.

8.5 Safety Monitoring Rules

Please refer also to the 'Guidance for Investigator' section of the Investigator's Brochure.

For the purposes of safety monitoring baseline is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 (e.g., qualification assessments or assessments from the final visits of ISIS 304801-CS6 and ISIS 304801-CS16 index studies if used for qualification).

In addition to the standard monitoring of clinical safety parameters, the following guidelines are provided for the monitoring of selected parameters chosen based on preclinical and clinical observations.

Confirmation Guidance: At any time during the study (Treatment or Post-Treatment Periods), the initial clinical laboratory results meeting the safety monitoring or stopping criteria presented below **must be confirmed** by performing measurements (ideally in the same laboratory that performed the initial measurement) on new specimens. All new specimen collections should take place as soon as possible (ideally within 3 days of the initial collection). For stopping rules, if the initial laboratory result is observed during the Treatment Period, the results from the retest **must be available** prior to administering the next dose of volanesorsen.

In addition to the safety monitoring parameters listed below, the Sponsor may request confirmation of additional lab values.

Re-dosing Guidance: Patients with initial laboratory test values that reach a stopping rule must not be re-dosed until the re-test results are available. In general, patients who do not meet the stopping rules based upon retest may continue dosing. However, the Investigator and the Sponsor Medical Monitor (or appropriately qualified designee) should confer as to whether additional close monitoring of the patient is appropriate. Reduction in dose or dose frequency may also be initiated as noted in Section 8.7. If any of the stopping criteria described below (refer to Sections 8.6.1 to 8.6.3) are met, the patient will be dose paused or permanently discontinued (as described in the stopping criterion concerned) from further treatment with volanesorsen, and evaluated fully as outlined below and in consultation with the Sponsor Medical Monitor or appropriately qualified designee, and will be followed up in accordance with Section 8.8 of the protocol.

8.5.1 Safety Monitoring for Liver Chemistry Tests

The following rules are adapted from the draft guidance for industry, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," issued by the U.S. Department of Health and Human Services, Food and Drug Administration, July 2009. For a definition of Baseline please refer to guidance in Section 8.5 above.

In the event of an ALT or AST measurement that is > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) at any time during the study (Treatment or Post-Treatment Period), the initial measurement(s) should be confirmed as described above. Additional confirmatory measurements should also be performed if ALT or AST levels increase to 5 x ULN.

Frequency of Repeat Measurements: Patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) should have their liver chemistry tests (ALT, AST, alkaline phosphatase (ALP), international normalized ratio (INR) and total bilirubin) retested at least once-weekly until ALT and AST levels become ≤ 1.2 x ULN or 1.2 x baseline value if the baseline value was > ULN.

Further Investigation into Liver Chemistry Elevations: For patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), the following evaluations should be performed:

1. Obtain a more detailed history of symptoms and prior and concurrent diseases
2. Obtain further history for concomitant drug use (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
3. Obtain a history for exposure to environmental chemical agents and travel
4. Serology for viral hepatitis (HAV IgM, HBsAg, HCV antibody, CMV IgM, and EBV antibody panel)
5. Serology for autoimmune hepatitis (e.g., antinuclear antibody [ANA])

Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic CT or MRI scans, may be performed at the discretion of the Investigator, in consultation with the Sponsor Medical Monitor. Repetition of the above evaluations should be considered if a patient's ALT and/or AST levels reach 5 x ULN.

8.5.2 Safety Monitoring for Platelet Count Results

Actions to be taken in the event of reduced platelet count are shown in Table 3 in Section 8.6.3.

The tests outlined in Table 2 should also be performed as soon as possible. Additional lab tests will be determined by the Sponsor Medical Monitor or designee in consultation with the Investigator.

Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor (See also Stopping Rules Section 8.6.3).

Table 2 Labs to Be Performed in the Event of a Platelet Count < 75,000/mm^3

Note: The following labs may change as additional data is assessed, and sites will be updated regarding any changes.

To Be Performed at Local Lab
Peripheral smear (should be performed locally, fixed and sent to central lab for review)
Fibrinogen split products or D-dimer on fresh blood
To Be Performed at Central Lab
Citrated sample for platelets
Coagulation panel (PT/INR, aPTT)
CBC with reticulocytes
Fibrinogen
von Willebrand factor
Total globulins, total IgA, IgG and IgM
Complement: total C3, total C4, Bb, C5a
hsCRP
Serology for:
HBV, HCV, HIV (if not done recently for screening)
Rubella
CMV
EBV
Parvo B19
Helicobacter pylori (IgG serum test)
Auto-antibody screen:
Antiphospholipid
Rheumatoid factor
Anti-dsDNA
Anti-thyroid
To Be Performed at Specialty Lab(s)
Antiplatelet antibodies and Anti-PF4 assay
Anti-ASO antibody

8.5.3 Safety Monitoring for Minor Bleeding Events

Minor bleeding events are those that do not fulfill the criteria for major bleeding or clinically-relevant, non-major bleeding events (which are defined in Section 8.6.3), for example excess bruising, petechiae, gingival bleeding on brushing teeth. If a minor bleeding event occurs, the Investigator must notify the Sponsor Medical Monitor and additional testing of coagulation parameters activated partial thromboplastin time (aPTT), prothrombin time (PT), INR and platelet count should be performed.

8.5.4 Safety Monitoring for Constitutional Symptoms

Patients will be instructed to promptly report any signs of symptoms of fever or constitutional symptoms that may arise during the study and the Investigator should closely evaluate all potential causes, including concomitant illness. Patients that experience persistent constitutional symptoms should be discussed with the Sponsor Medical Monitor or designee to determine whether additional monitoring or laboratory tests are required.

8.5.5 Safety Monitoring for LDL-C Elevations

Beginning at Week 13, laboratory alerts will be in place to notify the Investigator if a patient has a low-density lipoprotein-cholesterol (LDL-C) > 160 mg/dL (> 130 mg/dL for patients with T2DM) on 2 consecutive visits. If this occurs, LDL-C values for this patient will be unblinded for the remainder of the study and the Investigator will be encouraged to initiate/adjust treatment to lower LDL-C according to country-specific guidelines (e.g., initiate statin therapy or increase the statin dose for patients who are already on treatment).

8.5.6 Safety Monitoring for Insulin, Oral Antidiabetic Medication and Glucose

All patients on insulin will monitor their glucose levels with a glucometer as per standard practice guidelines and bring their glucometer or glucometer log printout to every clinic visit. In addition, patients who are not on insulin but use a glucometer should also bring their glucometer and/or glucometer log printout to every clinic visit.

- The Investigator or delegate will review the glucometer reading or printout at every clinic visit to evaluate if fasting pre-breakfast self-monitored plasma glucose values exceed threshold values as per the Safety Monitoring Rules for Hyperglycemia below.

All diabetic patients will note any changes in their insulin dose and /or oral antidiabetic therapy, as well as any hypoglycemic episode they may experience.

- The Investigator or delegate will ask patients at every clinic visit if they made changes in their insulin dose or oral antidiabetic therapy, and if they experienced a hypoglycemic episode.
    - Patients will be instructed on the monitoring and management of hypoglycemic episodes at each visit.
    - Documented symptomatic hypoglycemic episodes should be captured as adverse events in the adverse event CRF. Documented symptomatic hypoglycemia is defined as typical hypoglycemia symptoms accompanied by measured plasma glucose ≤ 70 mg/dL (≤ 3.9 mmol/L).
    - Any changes in insulin dose or oral antidiabetic therapy should be captured into the Concomitant Medication CRF.

8.5.7 Safety Monitoring for Documented Severe Hypoglycemia

A **documented severe hypoglycemic event** is defined as 1 in which the patient requires assistance of another person to obtain treatment for the event and has a plasma glucose level

≤ 70 mg/dL (≤ 3.9 mmol/L). The rescue treatment of hypoglycemia may include IV glucose or buccal or intramuscular glucagon.

The definition of severe symptomatic hypoglycemia includes all episodes in which neurological impairment was severe enough to prevent self-treatment and which were thus thought to place patients at risk for injury to themselves or others. Note that "requires assistance" means that the patient could not help himself or herself. Someone being kind that assists spontaneously the patient when not necessary does not qualify as "requires assistance."

Severe hypoglycemia will be qualified as a SAE only if it fulfills SAE criteria.

If a patient presents with symptoms of hypoglycemia, the Investigator will need to take immediate action to confirm the patient's glucose level and treat the patient accordingly.

The experience of hypoglycemia may vary greatly from patient to patient. However, there are certain classical signs and symptoms, of which patients should be aware as a clue that their blood glucose may be low. Common symptoms include headache, heart pounding, confusion, disorientation, numbness or tingling, pale skin, shakiness or tremulousness, increased appetite, anxiousness or nervousness, lightheadedness or dizziness, sweating, and weakness. Coma could occur if blood sugar correction is not performed.

If patients suspect they might be having a hypoglycemia reaction, they should check their blood glucose using their meters as soon as possible, before treatment if possible, provided they feel it is safe to do so. If there is doubt about safety they should treat the event first, using some sugar, milk, or juice for example, then obtain and record a blood glucose value as soon as possible thereafter. The time and nature of treatment should be noted, and especially if any blood glucose result was before or after treatment. It would be helpful for the patient to note if a contributory factor (e.g., missed or reduced meals, unaccustomed physical activity) occurred earlier in the day of the event.

8.5.8 Safety Monitoring for Hyperglycemia

Upward dose titration and/or addition of any other anti-hyperglycemic agent(s) will not be allowed during the course of the study, unless specific threshold values are met at Week 13 or later and confirmed on subsequent testing (ideally within 1-week of the initial test).

HbA1c is monitored every 3 months throughout the study. In addition, patients on insulin should self-monitor their plasma glucose (SMPG) routinely on a glucometer as per practice guidelines. If a fasting pre-breakfast SMPG value exceeds the specific glycemic limit, the patient should check it again on the following 2 days. If all the fasting pre-breakfast values on 3 consecutive days exceed the specific limit, the patient should contact the Investigator and an unscheduled central laboratory FPG measurement and HbA1c should be performed.

The threshold values are defined as:

- FPG > 270 mg/dL (15.0 mmol/L)
- HbA1c > 9% (for patients with baseline HbA1c < 8% and HbA1c increase of more than 1% from baseline (for patients with baseline HbA1c ≥ 8 and < 9%)

In case of confirmed FPG/HbA1c above the threshold value, the Investigator should ensure that no reasonable explanation exists for insufficient glucose control and in particular that:

- Plasma glucose was actually measured in the fasting condition (i.e., after at least 10 hours fast)
- Absence of intercurrent disease which may jeopardize glycemic control. In case of an emergency (e.g., surgery, infection), the Investigator can take appropriate measures for glycemic control
- Compliance to treatment is appropriate
- Compliance to diet and lifestyle is appropriate

If any of the above can reasonably explain the insufficient glycemic control, the Investigator should consider the following:

- Investigation and treatment of intercurrent disease (to be reported in adverse event (AE)/concomitant medication parts of the e-CRF)
- Stress on the absolute need to be compliant to treatment
- Organize a specific interview with a Registered Dietician or other qualified nutrition professional and stress on the absolute need to be compliant to diet and lifestyle recommendations

A FPG/HbA1c follow-up assessment should be arranged after appropriate action has been taken. If none from the above-mentioned reasons can be found, or if appropriate action fails to decrease FPG/HbA1c under the threshold values, additional medication may be introduced at the Investigator's discretion and according to local guidelines after discussion with the Sponsor Medical Monitor.

8.5.9 Acute Pancreatitis

If a patient has an episode of acute pancreatitis, dosing with Study Drug should be suspended temporarily until the patient is clinically stable. The suitability of the patient for continued dosing and the need for any modification to treatment schedule (refer to Section 8.7) will be determined by the Investigator in consultation with the Study Medical Monitor.

8.6 Stopping Rules

For the purposes of stopping rules baseline is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1.

8.6.1 Stopping Rules for Liver Chemistry Elevations

In the event of laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor,** dosing of a patient with volanesorsen will be stopped permanently; values that are not confirmed due to failure to retest or missing lab values will be presumed confirmed:

1. ALT or AST > 8 x ULN, which is confirmed
2. ALT or AST > 5 x ULN, which is confirmed and persists for ≥ 2 weeks
3. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed **and** total bilirubin > 2 x ULN or INR > 1.5
4. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed, and the new appearance (i.e., onset coincides with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> ULN) felt by the Investigator to be potentially related to hepatic inflammation

8.6.2 Stopping Rules for Renal Function Test Results

In the event of a persistent elevation that is observed over 2 consecutive weeks, for any of the 3 criteria below, dosing of a patient with volanesorsen may be stopped temporarily:

1. Serum creatinine increase that fulfill all of the following criteria: ≥ 0.3 mg/dL (26.5 µmol/L) and ≥ 40% above baseline creatinine values and > ULN
2. Proteinuria, dipstick 2 + (confirmed by dipstick retest and then further confirmed by a quantitative total urine protein measurement of > 1.0 g/24-hour)
3. Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault ≤ 40 mL/min that is confirmed by a 24-hour urine collection

The possible dosing re-initiation or follow-up schedule for any events meeting either of these criteria will be determined by the Investigator **in consultation with** the Sponsor Medical Monitor or designee.

8.6.3 Stopping Rules for Platelet Count Results

Actions to be taken in the event of a low platelet count are summarized in Table 3 below.

In the event of a platelet count less than 75,000/mm^3 that is associated with major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with volanesorsen will be stopped permanently. The follow-up schedule for any events meeting this stopping criterion will be determined by the Investigator in consultation with the Sponsor Medical Monitor.

In the event of any platelet count less than 25,000/mm^3, or a platelet count less than 75,000/mm^3 that occurs while the patient is on dosing at 300 mg every 2 weeks or 150 mg every week then dosing of a patient with volanesorsen will be stopped permanently. Platelet count will be monitored daily until 2 successive values show improvement then monitored every 2-3 days until platelet count is stable.

Administration of steroids is recommended for patients whose platelet count is less than 25,000/mm^3. Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one

0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (**note:** may require continuation with oral steroids after methylprednisolone).

In the event of a platelet count less than 75,000/mm^3, and in the absence of major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with volanesorsen should be suspended temporarily until the platelet count has recovered to> 100,000/mm^3. If dosing is continued it should be at a reduced dose frequency of 300 mg every 2 weeks or a reduced dose of 150 mg per week (refer to Section 8.7). The suitability of the patient for continued dosing will be determined by the Investigator in consultation with the Study Medical Monitor and will be based on factors such as the original rate of decline in the patient's platelet count, whether any bleeding events were experienced by the patient, and the speed of recovery of platelet count upon holding of dosing.

If after the first dosing rechallenge the platelet count again falls below 75,000/mm^3, then dosing of the patient with Study Drug will be stopped permanently.

Following a rechallenge platelet count should be tested every week until count is stable.

Any unreportable platelet count result must be rechecked and determined not to have met a stopping rule before dosing can continue.

If there is no reportable platelet count within 14 days of the last platelet count, the Investigator will contact the patient to hold dosing until a new platelet count is obtained and reviewed.

Definition of Major Bleeding Events (Schulman et al. 2005):

- Fatal bleeding, and/or
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarterial or pericardial, or intramuscular with compartment syndrome, and/or
- Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more within 24 hours, or leading to transfusion of 2 or more units of whole or red cells

Definition of Clinically-Relevant, Non-Major Bleeding Events (Schulman et al. 2005):

1. Multiple-source bleeding
2. Spontaneous hematoma > 25 cm^2
3. Excessive wound hematoma (not injection site related)
4. Macroscopic hematuria (spontaneous or lasting > 24 hours if associated with an intervention)
5. Spontaneous rectal bleeding; epitasis, gingival bleeding, hemoptysis, hematemesis
6. Bleeding after venipuncture for > 5 minutes

Table 3 Actions in Patients with Low Platelet Count

Platelet Count on Rx	Drug Dose	Monitoring
Normal range, > 140K/mm^3	No action	Monitor every 2 weeks
100K-140K/mm^3	No action	Closer observation Monitor every 1 week until stable*
75K-100K/mm^3	Permanently reduce dose frequency to 300 mg every 2 weeks or reduce dose to 150 mg weekly	Closer observation Monitor every 1 week
50K-75K/mm^3	If occurs while on dose of 300 mg every 2 weeks or 150 mg every week then permanently discontinue Study Drug, otherwise dose pause. When platelet count returns to > 100K/mm^3 restart dosing at dose frequency of 300 mg every 2 weeks or 150 mg weekly **only if approved by Sponsor Medical Monitor**	Closer observation Monitor every 2-3 days until 2 successive values show improvement Consider discontinuation of antiplatelet agents/NSAIDS/ anticoagulant medication
25K-50K/mm^3	If occurs while on dose of 300 mg every 2 weeks or 150 mg every week then permanently discontinue Study Drug, otherwise dose pause. When platelet count returns to > 100K/mm^3 restart dosing at dose frequency of 300 mg every 2 weeks or 150 mg weekly **only if approved by Sponsor Medical Monitor**	Closer observation Monitor daily until 2 successive values show improvement then monitor every 2-3 days until platelet count stable Discontinue antiplatelet agents/NSAIDS/anticoagulant medication while platelet count < 50K/mm^3 if possible
< 25K/mm^3	Permanently discontinue Study Drug	Closer observation: Monitor daily until 2 successive values show improvement then monitor every 2-3 days until platelet count stable Steroids recommended** Consider need for hospitalization and referral to hematologist Discontinue antiplatelet agents/NSAIDS/anticoagulant medication while platelet count < 50K/mm^3 if possible

* At least 3 consecutive values measured weekly that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3

** Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (**note**: may require continuation with oral steroids after methyl prednisolone)

8.7 Adjustment of Dose Frequency

Dose adjustments for platelet count reduction must be made in accordance with Section 8.6.3 and Table 3 (above).

Other dose adjustments, including dose interruptions, and/or decreasing the dose or dose frequency will be allowed for safety and tolerability. Any proposed adjustment to treatment

schedule must be discussed with, and approved by, the Study Medical Monitor prior to initiation. Up to 2 adjustments in the treatment schedule may be allowed.

Patients may be dose paused in response to AEs after consultation with Study Medical Monitor.

8.8 Discontinuation of Study Treatment

A patient must permanently discontinue study treatment for any of the following:

- The patient becomes pregnant. Report the pregnancy according to instructions in Section 9.5.4
- The patient withdraws consent
- The patient experiences an AE that necessitates permanent discontinuation of study treatment
- The patient develops laboratory test abnormalities that meet any of the stopping rules listed in Section 8.6

The reason for discontinuation of study treatment must be recorded in the CRF and source documentation.

8.8.1 Follow-up Visits for Early Termination from Treatment Period

Any patient who discontinues early from the Treatment Period should be followed as per the platelet monitoring rules shown in Table 3 in Section 8.6.3 for the first 6 weeks after discontinuing Study Drug. Following this period, if the platelet count is stable (at least 3 consecutive values that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3), the next platelet count should be taken within at least 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug. Patients should also be strongly encouraged to attend applicable landmark visits at Weeks 12, 13, 25, 26, and 50, 52 (calculated based on the time elapsed since Day 1) to collect fasting lipid panels and conduct safety assessments in accordance with the Schedule of Procedures in Appendix A. Any patient who discontinues treatment after Week 44 should also be strongly encouraged to attend a final follow-up visit (Week 65 visit assessments) approximately 13 weeks after their last dose of Study Drug, in addition to the applicable landmark visits.

If the patient declines or is unable to participate in the above, an early termination (ET) visit (Week 52 visit assessments) should be performed at the time of withdrawal, at a minimum, and ideally within 2 weeks from the last dose of Study Drug.

8.8.2 Follow-up Visits for Early Termination from Post-Treatment Follow-up Period

The patient who requests to withdraw from the study during the Post-Treatment Follow-up Period should be encouraged to follow the platelet monitoring rules shown in Table 3 in Section 8.6.3 for the first 6 weeks after discontinuing Study Drug. Following this period, if the platelet count is stable (at least 3 consecutive values that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3), the next platelet count should be taken within at least 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug.

Patients should also be encouraged to undergo a final follow-up visit (Week 65 (or Week 117 if terminating from the Extended Treatment Follow-Up Period), see Appendix A) prior to leaving the study.

If a patient withdraws due to an AE at any time during the study, the Investigator should arrange for the patient to have appropriate follow-up until the AE has resolved or stabilized.

8.9 Withdrawal of Patients from the Study

Patients must be withdrawn from the study for any of the following:

- Withdrawal of consent
- The patient is unwilling or unable to comply with the protocol

Other reasons for withdrawal of patients from the study might include:

- At the discretion of the Investigator for medical reasons
- At the discretion of the Investigator or Sponsor for noncompliance
- Significant protocol deviation

All efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information, including the reason for withdrawal from study, must be recorded in the CRF.

Any patient who withdraws consent to participate in the study will be removed from further treatment and study observation immediately upon the date of request. These patients should be encouraged to complete the ET study procedures and observations at the time of withdrawal (see Section 8.8 and Appendix A).

For patients withdrawn for reasons other than withdrawal of consent every effort should be made to complete the early termination study procedures and observations at the time of withdrawal (see Section 8.8 and Appendix A).

8.10 Concomitant Therapy and Procedures

The use of concomitant therapies or procedures defined below must be recorded on the patient's CRF. AEs related to administration of these therapies or procedures must also be documented on the appropriate CRF.

8.10.1 Concomitant Therapy

A concomitant therapy is any non-protocol specified drug or substance (including over-the-counter medications, herbal medications and vitamin supplements) administered between signing informed consent and completion of the post-treatment follow-up period. All concomitant medications/treatments and significant non-drug therapies (including supplements and assistive devices) received by a patient, including changes in the patient's current medications, must be recorded in the patient's source documents and CRF. Patients taking over the counter (OTC) omega-3 fatty acids should make every effort to remain on the same brand throughout the study.

Allowed Concomitant Therapy

Any medications deemed necessary by the Investigator are allowed except those listed in the disallowed concomitant therapy.

Disallowed Concomitant Therapy

No lipid lowering therapies (e.g., fibrates, niacin, fish oil or other products containing omega-3 fatty acids [including OTC preparations]), -glucagon-like peptide-1 (GLP-1) agonists, Glybera, or systemic corticosteroids may be started or adjusted after baseline qualification. Doses of existing oral anti-diabetic medication, oral contraceptives, hormone replacement therapy, anticoagulants, or drugs or dietary supplements with potential lipid-altering effects should not be adjusted. Study patients are prohibited from receiving other experimental agents during the study. This includes marketed agents at experimental dosages that are being tested for the treatment of hypertriglyceridemia.

Patients should consult with the Site Investigator or designee prior to initiating any new medication, including non-prescription or herbal compounds or any other non-drug therapy.

8.10.2 Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between signing of informed consent and Week 65 (or Week 117 if patient enters the extended treatment period) visit.

Disallowed Concomitant Procedure

Plasma apheresis is not allowed during the study.

8.11 Treatment Compliance

Compliance with treatment dosing is to be monitored and recorded by Study Center staff. The Study Center staff is required to document the receipt, dispensing, and return/destruction of volanesorsen. Patients that are self-administering volanesorsen at home must record treatment in a dosing diary that will be reviewed periodically by Study Center staff and the Clinical Monitor.

9. SERIOUS AND NON-SERIOUS ADVERSE EVENT REPORTING

9.1 Sponsor Review of Safety Information

Safety information will be collected, reviewed, and evaluated by the Sponsor in accordance with the Safety Management Plan throughout the conduct of the clinical trial.

9.2 Regulatory Requirements

The Sponsor is responsible for regulatory submissions and reporting to the Investigators of serious adverse events (SAEs) including suspected unexpected serious adverse reactions (SUSARs) per the International Conference on Harmonization (ICH) guidelines E2A and ICH E6. Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines.

Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) will be notified of any SAE according to applicable regulations. The Independent DSMB will be notified of any SAE as specified in the DSMB charter.

In addition to the Investigator's assessment of relatedness, the Sponsor or designee will evaluate the available information and perform an independent assessment of relatedness. While the Sponsor may upgrade an Investigator's decision it is not permissible to downgrade the Investigator's opinion for the purposes of determining whether the SAE meets the definition of a SUSAR.

The following table identifies the SAEs that the Sponsor or designee will not report on an individual basis in an expedited manner because they are anticipated to occur in the study population independent of volanesorsen exposure. The Investigator still has the responsibility to report all SAEs to the Sponsor as described in Sections 9.4.1 to 9.4.3.5.

Table 4 Expected Event for the Protocol Defined Population by Preferred Term and the Expected Incidence

Preferred Term	Expected Incidence in the Protocol Defined Population (Gaudet et al. 2010 and 2013)
Pancreatitis associated events including the PTs of hereditary pancreatitis, pancreatitis, pancreatitis acute, pancreatitis chronic, pancreatitis necrotizing, pancreatitis relapsing	0.2-0.35 events per patient-year

Fatal pancreatitis associated events will be considered as unexpected and are reportable. The Sponsor and DSMB will monitor non-fatal pancreatitis associated SAEs using the incidence rate of the event compared to the rate expected in a non-volanesorsen exposed population. If the aggregate analysis indicates that an event is occurring significantly more frequently or at a greater severity than expected, then the event will be reported.

SAEs not specified in the table will be evaluated on case by case basis to determine whether there is a reasonable possibility that the drug caused the event. If the event is considered by the Sponsor or designee to meet the definition of a SUSAR the event will be reported.

9.3 Definitions

9.3.1 Adverse Event

An adverse event is any unfavorable and unintended sign (including a clinically-significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the study or use of investigational drug product, whether or not the AE is considered related to the investigational drug product.

9.3.2 Adverse Reaction and Suspected Adverse Reaction

An adverse reaction is any adverse event caused by volanesorsen.

A suspected adverse reaction is any adverse event for which there is a reasonable possibility that volanesorsen drug caused the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

9.3.3 Serious Adverse Event (SAE)

A serious adverse event is any adverse event that in the view of either the Investigator or Sponsor, meets any of the following criteria:

- Results in death
- Is life threatening: that is, poses an immediate risk of death at the time of the event

An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Hospitalization is defined as an admission of greater than 24 hours to a medical facility and does not always qualify as an AE
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly or birth defect in the offspring of the patient (whether the patient is male or female)
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

9.4 Monitoring and Recording Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the study (i.e., before informed consent) should be recorded as Medical History and not recorded as AEs unless the pre-existing condition worsened. The Investigator should always group signs and symptoms into a single term that constitutes a **single unifying diagnosis** if possible.

9.4.1 Serious Adverse Events

In the interest of patient safety, and in order to fulfill regulatory requirements**,** all SAEs (regardless of their relationship to volanesorsen) should be reported to the Sponsor or designee within 24 hours of the Study Center's first knowledge of the event. The collection of SAEs will begin after the patient signs the informed consent form and stop at the end of the patient's

follow-up period which is defined as the Week 65 visit. When the Investigator is reporting by telephone, it is important to speak to someone in person versus leaving a message. An Initial Serious Adverse Event Form should be completed and a copy should be faxed to the Sponsor or designee.

Detailed information should be actively sought and included on Follow-Up Serious Adverse Event Forms as soon as additional information becomes available. All SAEs will be followed until resolution. SAEs that remain ongoing past the patient's last protocol-specified follow-up visit will be evaluated by the Investigator and Sponsor. If the Investigator and Sponsor agree the patient's condition is unlikely to resolve, the Investigator and Sponsor will determine the follow-up requirement.

9.4.2 Non-Serious Adverse Events

The recording of non-serious AEs will begin after the patient signs the informed consent form and will stop at the end of the patient's follow-up period, which is defined as the Week 65 visit (or Week 117 if patient enters the extended treatment period). The Investigator will monitor each patient closely and record all observed or volunteered AEs on the Adverse Event Case Report Form.

9.4.3 Evaluation of Adverse Events (Serious and Non-Serious)

The Investigator's opinion of the following should be documented on the Adverse Event Case Report Form:

9.4.3.1 Relationship to the Study Drug

The event's relationship to volanesorsen is characterized by 1 of the following:

- **Related:** There is clear evidence that the event is related to the use of volanesorsen, e.g., confirmation by positive rechallenge test
- **Possible:** The event cannot be explained by the patient's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and volanesorsen administration
- **Unlikely/Remote:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to volanesorsen administration and/or exposure suggests that a causal relationship is unlikely (For reporting purposes, Unlikely/Remote will be grouped together with Not Related)
- **Not Related:** The event can be readily explained by the patient's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and volanesorsen

9.4.3.2 Severity

The severity of AEs and SAEs will be graded based on criteria from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010 (refer to Appendix D). Any AE not listed in Appendix D will be graded as follows:

- **Mild:** The event is easily tolerated by the patient and does not affect the patient's usual daily activities
- **Moderate:** The event causes the patient more discomfort and interrupts the patient's usual daily activities
- **Severe:** The event is incapacitating and causes considerable interference with the patient's usual daily activities

If the event is an SAE, then all applicable seriousness criteria must be indicated (criteria listed in Section 9.3.3).

9.4.3.3 Action Taken with Volanesorsen

Action taken with volanesorsen due to the event is characterized by 1 of the following:

- **None:** No changes were made to volanesorsen administration and dose
- **Permanently Discontinued:** Volanesorsen was discontinued and not restarted
- **Temporarily Interrupted, restarted – same dose:** Dosing was temporarily interrupted or delayed due to the AE and restarted at the same dose
- **Reduced schedule:** Dosing frequency was reduced

9.4.3.4 Treatment Given for Adverse Event

Any treatment (e.g., medications or procedures) given for the AE should be recorded on the Adverse Event Case Report Form (treatment should also be recorded on the concomitant treatment or ancillary procedures CRF as appropriate).

9.4.3.5 Outcome of the Adverse Event

If the event is a non-serious AE then the event's outcome is characterized by 1 of the following:

- **AE Persists:** Patient terminates from the trial and the AE continues
- **Recovered:** Patient recovered completely from the AE
- **Became Serious:** The event became serious (the date that the event became serious should be recorded as the Resolution Date of that AE and the Onset Date of the corresponding SAE)
- **Change in Severity** (if applicable): AE severity changed

If the event is a SAE then the event's outcome is characterized by 1 of the following:

- **Ongoing:** SAE continuing
- **Persists (as non-serious AE):** Patient has not fully recovered but the event no longer meets serious criteria and should be captured as an AE on the non-serious AE eCRF (the SAE resolution date should be entered as the date of onset of that AE)

- **Recovered:** Patient recovered completely from the SAE (the date of recovery should be entered as the SAE resolution date)

- **Fatal:** Patient died (the date of death should be entered as the SAE resolution date)

9.4.4 Adjudication Committees

All SAEs that occur during the study that are consistent with a major acute cardiovascular event (MACE) will be adjudicated by a blinded, independent committee as outlined in the MACE Adjudication Charter.

All AEs and SAEs that occur during the study that are consistent with an event of acute pancreatitis will be adjudicated by a blinded, independent committee according to the Atlanta classification of acute pancreatitis (Banks et al. 2013) and as outlined in the Pancreatitis Adjudication Charter. In addition, data for prior episodes of acute pancreatitis or suspected pancreatitis will be collected by review of each patient's medical chart and these events will also be adjudicated.

9.5 Procedures for Handling Special Situations

9.5.1 Abnormalities of Laboratory Tests

Clinically-significant abnormal laboratory test results may, in the opinion of the Investigator, constitute or be associated with an AE. Examples of these include abnormal laboratory results that are associated with symptoms, or require treatment, e.g., bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac arrhythmias due to hyperkalemia. Whenever possible, the underlying diagnosis should be listed in preference to abnormal laboratory values as AEs. Clinically-significant abnormalities will be monitored by the Investigator until the parameter returns to its baseline value or until agreement is reached between the Investigator and Sponsor Medical Monitor. Laboratory abnormalities deemed not clinically-significant (NCS) by the Investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator should not be deemed NCS on the laboratory sheet.

The Investigator is responsible for reviewing and signing all laboratory reports. The signed clinical laboratory reports will serve as source documents and should include the Investigator's assessment of clinical significance of out of range/abnormal laboratory values.

9.5.2 Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the patient is hospitalized; the Study Center must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the patient's consent to participate in the study

- The condition that required the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the patient's consent to participate in the study and the timing of the procedure or treatment

- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission

9.5.3 Dosing Errors

Volanesorsen dosing errors should be documented as Protocol Deviations. A brief description should be provided in the deviation, including whether the patient was symptomatic (list symptoms) or asymptomatic, and the event accidental or intentional.

Dosing details should be captured on the Dosing Case Report Form. If the patient takes a dose of volanesorsen that exceeds protocol specifications and the patient is symptomatic, then the symptom(s) should be documented as an AE and be reported per Section 9.4.

Should an overdose occur, the Investigator or designee should refer to the Guidance to Investigator's section of the Investigator's Brochure and contact the Sponsor or designee within 24 hours.

9.5.4 Contraception and Pregnancy

Male patients and female patients of childbearing potential must continue to use appropriate contraception with their partners, or refrain from sexual activity, as described in Section 6.3.1.

If a patient becomes pregnant or a pregnancy is suspected, or if a male patient makes or believes that he has made someone pregnant during the study, then the Study Center staff must be informed immediately. An Initial Pregnancy Form should be submitted to the Sponsor or designee **within 24 hours** of first learning of the occurrence of pregnancy. Follow-up information including delivery or termination is reported on Follow-up Pregnancy Forms and reported within 24 hours.

Payment for all aspects of obstetrical care, child or related care will be the patient's responsibility.

Female patients: If a suspected pregnancy occurs while on the study (including follow-up), a pregnancy test will be performed. The patient with a confirmed pregnancy will be immediately withdrawn from treatment with volanesorsen. However, the patient will be encouraged to complete the post-treatment follow-up portion of the study to the extent that study procedures do not interfere with the pregnancy. Regardless of continued study participation, the study physician will assist the patient in getting obstetrical care and the progress of the pregnancy will be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the Study Center and Sponsor may require access to the mother and infant's medical records for an additional 8 weeks after birth.

Male patients: The progress of the pregnancy in a male patient's partner should be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, **the Study Center and Sponsor may request access to the mother and infant's medical records for an additional 8 weeks after birth**. Follow-up will be performed to the extent permitted by applicable regulations and privacy considerations.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints

For fasting lipid measurements, the values at Month 3 analysis time point are defined as the average of Week 12 (Day 78) and Week 13 (Day 85) fasting assessments, the values of Month 6 analysis time point is at the end of Month 6 are defined as the average of Week 25 (Day 169) and Week 26 (Day 176) fasting assessments, and the values at the Month 12 analysis time point are defined as the average of Week 50 (Day 344) and Week 52 (Day 358) fasting assessments.

10.1.1 Efficacy Endpoints

- Percent change and absolute change from baseline in fasting TG
- Frequency and severity of patient reported abdominal pain during the treatment period
- Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-HDL-C, apoB, HDL-C, apolipoprotein A-1 (apoA-1), VLDL-C, and LDL-C
- Percent change from baseline in fasting total apolipoprotein C-III
- Quality of Life questionnaires (EQ-5D, SF-36)
- Adjudicated acute pancreatitis event rate
- Other symptoms: eruptive xanthoma, lipemia retinalis

10.1.2 Safety Endpoints

- Adverse events including adjudicated events of pancreatitis and MACE
- Vital signs and weight
- Physical examinations
- Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis)
- Echocardiography
- Electrocardiograms (ECGs)
- Use of concomitant medications
- MRIs

10.2 Sample Size

No sample size calculations were performed as this is an open-label study.

10.3 Populations

Full Analysis Set (FAS): All patients who are enrolled and received at least 1 dose of active Study Drug and have a baseline TG assessment. The FAS represents the practically-feasible intent-to-treat (ITT) population as delineated in ICH Guideline E9.

Per Protocol Set (PPS): Subset of the FAS who received 9 of first 13 scheduled doses of volanesorsen and with no significant protocol deviations that would be expected to affect efficacy and PD assessments. The detailed criteria will be specified and finalized prior to the final database lock.

Safety Set: All patients who are enrolled and receive at least 1 dose of volanesorsen.

PK Population: All patients who are enrolled, receive at least 1 dose of volanesorsen, and have at least 1 post first dose PK sample collected, analyzed, and reported.

10.4 Definition of Baseline

Definitions of baseline are given below for the purposes of the final analysis.

For fasting lipid measurements, 2 baselines are defined for each patient in Groups 1 and 2: Group 1 (ISIS 304801-CS6) or Group 2 (ISIS 304801-CS16) index study baseline and the baseline in this open-label study, which is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 (e.g., qualification assessments or assessments from final visit of the ISIS 304801-CS6 or ISIS 304801-CS16 index studies if used for qualification). For Group 3 patients, the baseline for fasting lipid measurements is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 in this open-label study.

For other measurements, baseline for patients on active treatment in the ISIS 304801-CS6 or ISIS 304801-CS16 index study will be the ISIS 304801-CS6 or ISIS 304801-CS16 index study baseline. For patients on placebo in the ISIS 304801-CS6 or ISIS 304801-CS16 index study and Group 3 patients, baseline will be the last non-missing assessment prior to the first dose of Study Drug.

10.5 Interim Analysis

An interim analysis may be conducted after the last patient's Week 13 visit of the open-label study or after the database of the ISIS 304801-CS6 and ISIS 304801-CS16 index studies are locked and unblinded. Both safety and efficacy information from this open-label study may be summarized during this interim analysis. Efficacy analyses will be detailed in the SAP.

10.6 Planned Methods of Analysis

All eCRF data, lab data transfers, as well as any outcomes derived from the data, will be provided in the patient data listings. Patient data listings will be presented for all patients enrolled into the study. Descriptive summary statistics including n, mean, median, standard deviation, standard error, interquartile range (25th percentile, 75th percentile), and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data by treatment group of the index studies for patients on active in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies, and pooled treatment naive group which including patients on placebo in index studies and Group 3 patients.

Where appropriate, p-values will be reported. All statistical tests will be conducted using 2-sided tests with 5% Type I error rates unless otherwise stated.

TG related endpoints will be assessed in the FAS and PPS, and all other efficacy endpoints will be assessed in the FAS. All safety assessments will be performed on the Safety Set. PK endpoints will be assessed in the PK Set as applicable.

10.6.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics by treatment group and overall. The patient disposition will be summarized by treatment group and overall. All patients enrolled will be included in a summary of patient disposition.

10.6.2 Safety Analysis

Treatment duration and amount of Study Drug received will be summarized by treatment group and overall.

Patient incidence rates of AEs will be tabulated by MedDRA system organ class, MedDRA preferred term, and treatment group of the index studies. Narratives of treatment-emergent deaths, serious and significant AEs, including early withdrawals due to AEs, will also be provided.

All treatment-emergent AEs, all treatment-emergent AEs potentially related to Study Drug, all treatment-emergent serious AEs, and all treatment-emergent serious AEs potentially related to Study Drug will be summarized.

Injection Site Reactions (ISRs) will be summarized by treatment group, MedDRA preferred term and severity.

Independently adjudicated events of MACE and pancreatitis will be summarized by treatment group.

Laboratory tests to ensure patient safety including chemistry panel, complete blood count (CBC) with differential, coagulation panel, IM, complement etc., will be summarized by study visits by treatment group.

These safety variables will also be presented as change and percent change from baseline over time after Study Drug administration, as appropriate.

Vital signs, weight, ECG measures, echocardiography assessments, and MRI assessments will be tabulated by treatment group.

10.6.3 Efficacy Analysis

Percent change and change from baseline to Month 3, Month 6, and Month 12 in fasting TG will be summarized by treatment group. Response rate of patients with fasting plasma TG < 750 mg/dL or achieving fasting TG $\geq 40\%$ reduction from baseline at Month 3, Month 6, and Month 12 will be summarized. Response analysis will also be conducted using a range of fasting plasma TG thresholds for determination of responder status.

Percent change and change from baseline to Month 3, Month 6, and Month 12 will also be summarized by treatment group for other fasting lipid measures including non-HDL-C, apoB, HDL-C, apoA-1, VLDL-C, and LDL-C, total cholesterol, and fasting total apoC-III.

The incremental effects of volanesorsen on lipid measures will be explored and the association between changes in lipid parameters and total amount of drug received will be examined, as appropriate.

Frequency and severity of patient reported abdominal pain, adjudicated acute pancreatitis event rate, quality of life assessments, and comparison of other symptoms including eruptive xanthomas and lipemia retinalis will be summarized by treatment group.

Additional details of the analyses to be conducted will be provided in the SAP.

10.6.4 Pharmacokinetic and Immunogenicity Analysis

10.6.4.1 Pharmacokinetic Analysis

For all patients, pre-dose and post-treatment volanesorsen plasma concentrations will be summarized using descriptive statistics by treatment group and IM status.

For patients in the PK subgroup only, non-compartmental PK analysis of volanesorsen will be carried out on each individual patient data set using data collected in the open-label study from the intensive PK subgroup, following a single-dose (i.e., single-dose PK) or multiple doses (i.e., steady-state PK), depending on their earlier treatment in the index studies (Group 1 and 2 patients). On Week 1 Day 1 of the open-label study, patients who received placebo in the index study (and all patients in Group 3) will receive the first treatment of volanesorsen (single-dose PK), while patients who received volanesorsen in the index studies had been on volanesorsen treatment for 12 months (ISIS 304801-CS6) or 6 months (ISIS 304801-CS16), thus the PK data collected from these patients reflect steady-state PK. The maximum observed drug concentration (C_{max}) and the time taken to reach C_{max} (T_{max}) will be obtained directly from the concentration-time data. Area under the plasma concentration-time curve from time zero to 24 hours ($AUC_{0\text{-}24h}$) will be calculated using the linear trapezoidal rule. Apparent systemic (plasma) clearance after SC administration ($CL_{0\text{-}24h}$ /F) will be calculated from $CL_{0\text{-}24h}/F$ = Actual Dose/$AUC_{0\text{-}24h}$. Mean residence time (MRT) from time zero to 24 hours after the SC administration will be calculated from the equation, $MRT_{0\text{-}24h} = AUMC_{0\text{-}24h}/AUC_{0\text{-}24h}$, where $AUMC_{0\text{-}24h}$ is the area under the moment plasma concentration-time curve from time zero to 24 hours after the SC administration. Other PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist.

Plasma PK parameters will be summarized using descriptive statistics by treatment group and IM status. Additional details regarding the PK analysis will be described in the SAP.

Population PK, PK/PD, and covariate analysis may be performed if deemed appropriate, and results will be reported separately.

10.6.4.2 Immunogenicity Analysis

Immunogenicity (IM) results (screen positive/negative, confirmed positive/negative or not evaluable, and when applicable, titer of anti-volanesorsen antibodies) before, during, and after

treatment with Study Drug (volanesorsen) (i.e., sample [anti-drug antibody] ADA status) will be listed by their prior treatment in study ISIS 304801-CS6 or ISIS 304801-CS16 (Groups 1 and 2) and study day. Subject ADA status (positive/negative or not evaluable) for all evaluable patients, along with the study day associated with the first positive IM status emerged (T_{first}, i.e., onset of ADA development), the last positive IM status observed (T_{last}), the last ADA sample collection day, and subject - peak titer if applicable, will be listed by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16 (Groups 1 and 2) and study day. Subjects with positive anti-volanesorsen antibody status may be further classified (when applicable) as being either 'persistent', 'transient', or 'not determinable', if deemed appropriate.

Additionally, the sample and subject IM incidence (number) and incidence rate (percent) will be summarized as the total number and percent of evaluated subjects with antibody negative, positive, and unknown status by treatment group. Furthermore, onset and titer of the ADA response, if applicable, will be summarized as median, quartiles (25% and 75%), and range.

Additional details regarding the IM data analysis will be described in the SAP.

Potential relationships between immunogenicity results (e.g., IM status) and selected efficacy (e.g., % change in fasting TG from baseline at 3-, 6-, and 12-month endpoints), safety, and PK (e.g., C_{trough}) measures will be evaluated using graphical analysis and statistical analysis. These analyses will be either conducted and included in the study report, or data pooled and analyzed from all available Phase 2 and 3 studies and reported separately.

11. INVESTIGATOR'S REGULATORY OBLIGATIONS

11.1 Informed Consent

The written informed consent document should be prepared in the language(s) of the potential patient population, based on an English version provided by the Sponsor.

Before a patient's participation in the trial, the Investigator is responsible for obtaining written informed consent from the patient after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific qualification procedures or any Study Drug are administered. The patient must be given sufficient time to consider whether to participate in the study.

The acquisition of informed consent and the patient's agreement or refusal to notify his/her primary care physician should be documented in the patient's medical records and the informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion (not necessarily an Investigator). The original signed informed consent form should be retained in the Study Master File and in any other locations required by institutional policy, and a copy of the signed consent form should be provided to the patient.

11.2 Ethical Conduct of the Study

The Guidelines of the World Medical Association (WMA) Declaration of Helsinki dated October 2002 the applicable regulations and guidelines of current Good Clinical Practice (GCP)

as well as the demands of national drug and data protection laws and other applicable regulatory requirements will be strictly followed.

11.3 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent form, other written patient information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by the Sponsor before recruitment of patients into the study and shipment of volanesorsen. A copy of the written approval of any other items/materials that must be approved by the Study Center or IEC/IRB must also be received by the Sponsor before recruitment of patients into the study and shipment of Study Drug. The Investigator's Brochure must be submitted to the IEC/IRB for acknowledgement.

The Investigator must submit to and, where necessary, obtain approval from the IEC/IRB, for all subsequent protocol amendments and changes to the informed consent document. The Investigator should notify the IEC/IRB of deviations from the protocol in accordance with ICH GCP Section 4.5.2. The Investigator should also notify the IEC/IRB of serious adverse events occurring at the Study Center and other adverse event reports received from the Sponsor, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study. Copies of the Investigator's reports, all IEC/IRB submissions and the IEC/IRB continuance of approval must be sent to the Sponsor.

11.4 Patient Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained. On the case report forms (CRF) or other documents submitted to the Sponsor, patients should be identified by unique initials and a patient study number only. Documents that are not for submission to the Sponsor (e.g., signed informed consent forms) should be kept in strict confidence by the Investigator.

In compliance with Federal and local regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the patient to permit named representatives to have access to his/her study-related records without violating the confidentiality of the patient.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments

Protocol amendments must be made only with the prior approval of the Sponsor. Agreement from the Investigator must be obtained for all protocol amendments and amendments to the informed consent document. The regulatory authority and IEC/IRB must be informed of all amendments and give approval for any amendments likely to affect the safety of the patients or

the conduct of the trial. The Investigator **must** send a copy of the approval letter from the IEC/IRB to the Sponsor.

12.2 Study Termination

The Sponsor reserves the right to terminate the study according to the terms of the site contract. The Investigator reserves the right to terminate their participation in the study, according to the terms of the site contract. The Investigator/Sponsor should notify the IEC/IRB in writing of the trial's completion or early termination and send a copy of the notification to the Sponsor.

12.3 Study Documentation and Storage

An electronic case report form (eCRF) utilizing an Electronic Data Capture (EDC) application will be used for this study.

The Investigator should ensure that all appropriately qualified persons to whom he/she has delegated trial duties are recorded on a Sponsor-approved Delegation of Site Responsibilities Form.

Source documents are original documents, data, and records from which the patient's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, imaging, and correspondence. In this study, CRFs may not be used as source documents.

The Investigator and Study Center staffs are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation in accordance with Section 8 of the ICH Guidelines (E6), suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Elements should include:

- Patient files containing completed CRFs, informed consents, and supporting copies of source documentation
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation and all correspondence to and from the IEC/IRB and the Sponsor
- If volanesorsen supplies are maintained at the Study Center, proof of receipt, volanesorsen Accountability Record, Return of volanesorsen for Destruction, final study volanesorsen reconciliation, and all volanesorsen-related correspondence

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

No study document should be destroyed without prior written agreement between the Sponsor or and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor.

12.4 Study Monitoring

The Sponsor representative and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the trial (e.g., CRFs and other pertinent data) provided that patient confidentiality is respected.

The Sponsor monitor is responsible for inspecting the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to patient medical records and other study-related records needed to verify the entries on the CRFs.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's Clinical Quality Assurance Department. Inspection of Study Center facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the trial conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

To ensure the quality of clinical data a clinical data management review will be performed on patient data received by the Sponsor. During this review, patient data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or Study Center notifications will be sent to the Study Center for completion and return to Sponsor.

The Principal Investigator will sign and date the indicated places on the CRF. These signatures will indicate that the principal Investigator inspected or reviewed the data on the CRF, the data queries, and the Study Center notifications, and agrees with the content.

12.5 Language

Case report forms must be completed in English. Generic names for concomitant medications should be recorded in English if possible, unless it is a combination drug, then record the trade name in English.

All written information and other material to be used by patients and investigative staff must use vocabulary and language that are clearly understood.

12.6 Compensation for Injury

The Sponsor maintains appropriate insurance coverage for clinical trials and will follow applicable local compensation laws. Patients will be treated and/or compensated for any study-related illness/injury in accordance with the information provided in the Compensation for Injury section of the Informed Consent document.

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14. APPENDICES

Appendix A Schedule of Procedures

Appendix A Schedule of Procedures

Study Period		Screen/ Run In[a]	Qual[a]	Treatment Period																								Post Treatment Follow-up		
Study Week		-8 to -2	-2 to -1	Wk 1		Wk 2.5	Wk 4	Wk 6	Wk 8	Wk 10	Month 3		Wk 15 & 17	Wk 19	Wk 21 & 23	Month 6		Wk 28 & 30	Wk 32	Wk 34 & 36	Wk 38	Wk 40 & 42	Wk 44	Wk 46 & 48	Month 12		Wk 54 & 56	Wk 58	Wk 65
											Wk 12	Wk 13				Wk 25	Wk 26								Wk 50	Wk 52 or ET			
Study Day		-56 to -15	-14 to -7	1	2	11	22	36	50	64	78	85	99 & 113	127	141 & 155	169	176	190 & 204	218	232 & 246	260	274 & 288	302	316 & 330	344	358	372 & 386	400	449
Visit Window+/- Days		0	0	0	0	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	7	7
Informed Consent		X	X																											
Outpatient Visit		X	X	X	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X	X[l]	X[l]	X[l]	X[l]	X	X[l]	X[l]	X[l]	X	X[l]	X[l]	X[l]	X[l]	X	X[l]	X[l]	X
Inclusion/Exclusion Criteria		X	X																											
Medical History[b]		X																												
Vital Signs + body weight (+ height on Day 1 only)		X	X	X			X		X			X					X				X					X			X
Physical Examination		X		X								X					X				X					X			X
12- lead ECG (triplicate)		X										X					X				X					X			X
MRI (liver/spleen)		X																								X[m]			
Echocardiography		X															X[m]									X[m]			
Blood Draw (Fasting)[d]	Chemistry Panel	X	X	X			X		X			X		X			X		X		X		X			X		X	X
	CBC with Differential[c]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Serum Lipid Panel	X	X	X			X		X		X	X				X	X				X				X	X			X
	Coagulation (aPTT, PT, INR)	X	X						X			X					X				X					X			
	Hepatitis B, C, HIV	X																												
	hsCRP, HbA1c, FPG, and de-lipidated free glycerol			X								X					X									X			X
	Sedimentation Rate			X								X					X									X			X
	Complement (C5a, Bb)			X								X					X									X			X
	Troponin I	X		X								X					X									X			X
	Platelet Bound Autoantibodies[e]			X																										
	Plasma PK - Volanesorsen			X[n]	X		X		X			X					X				X					X			X
	Anti-Volanesorsen Antibodies			X			X		X			X					X				X					X			X
	FSH (women only, if applicable)	X																												
	Serum Pregnancy Test[f]	X	X				X		X			X		X			X		X		X		X			X		X	X
	Archived Serum & Plasma Samples[g]			X					X			X					X									X			X

Appendix A Schedule of Procedures *Continued*

Study Period	Screen/ Run In[a]	Qual[a]	Treatment Period																								Post Treatment Follow-up		
Study Week	-8 to -2	-2 to -1	Wk 1		Wk 2.5	Wk 4	Wk 6	Wk 8	Wk 10	Month 3		Wk 15 & 17	Wk 19	Wk 21 & 23	Month 6		Wk 28 & 30	Wk 32	Wk 34 & 36	Wk 38	Wk 40 & 42	Wk 44	Wk 46 & 48	Month 12		Wk 54 & 56	Wk 58	Wk 65
										Wk 12	Wk 13				Wk 25	Wk 26								Wk 50	Wk 52 or ET			
Study Day	-56 to -15	-14 to -7	1	2	11	22	36	50	64	78	85	99 & 113	127	141 & 155	169	176	190 & 204	218	232 & 246	260	274 & 288	302	316 & 330	344	358	372 & 386	400	449
Visit Window+/- Days	0	0	0	0	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	7	7
Urinalysis[d]	X	X	X[o]			X		X			X[o]		X[o]			X[o]		X[o]		X[o]		X[o]			X[o]		X[o]	X[o]
Fundus Photography[h]	X																								X[m]			
Genetic testing for FCS diagnosis (if not available in medical history)[i]	X																											
Weekly Study Drug: SC Injection			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Symptom Diary (weekly)	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Assessment(s)			X								X					X									X			X
Food/Drink Diary (quarterly)[j]			X								X					X									X			X
Diet/Alcohol Counseling[k]	X	X	X			X		X			X					X				X					X		X	X
Adverse Events	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a Screening and Qualification (Group 3) procedures performed (Please refer to Sections 3.4, 4.1, and 6.1.2)

b Patient charts will be reviewed in order to collect data for events of acute pancreatitis or suspected pancreatitis in the patient's medical history. Chart review may be conducted at any time during the study. These events will be adjudicated in the same manner as for events of pancreatitis during the study

c Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1 week and determined not to have met a stopping rule before dosing can continue. If there is no reportable platelet count within 14 days of the last platelet count, the Investigator will contact the patient to hold dosing until a new platelet count is obtained and reviewed. All platelet count results will be promptly reviewed by the Investigator to ensure that the count has not met the stopping rule and to determine whether the rate of decline is suggestive that the patient could be approaching the dose pause rule of 75,000/mm^3. Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor

Appendix A Schedule of Procedures *Continued*

Legend Text *Continued*

d Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours. During treatment period urine and blood samples will be collected prior to Study Drug administration. Does not apply to 24-hour PK blood draw

e May be done

f Females of childbearing potential only

g Serum and plasma samples will be collected and stored for follow-up exploration of laboratory findings and/or adverse events (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.) in this or subsequent clinical studies of volanesorsen

h If possible, fundus photography should be completed prior to administration of the first dose of Study Drug (Group 2 [ISIS 304801-CS16 roll-over patients] and Group 3) and repeated at Week 52 (Please refer to Section 6.2.2.2)

i Genetic testing can be conducted for study qualification (Group 2 [ISIS 304801-CS16 roll-over patients] and Group 3); genetic testing will only be conducted if allowed in the geographic region and only after the patient has given specific written informed consent for genetic testing

j In addition to diary, patients will be contacted at random times during the study to review their current eating and drinking habits

k To reinforce compliance to the diet and alcohol restrictions. Random diet/alcohol assessments (phone visits) will also be performed by dietician or study personnel

l Assessments and procedures to be conducted by either a home healthcare nurse, or the Study Center as arranged by the Study Center personnel

m A ± 7-day window is allowed for MRI, echocardiography procedures and fundus photography

n Full or abbreviated PK profile (see Appendix C)

o Expanded urinalysis (see Appendix B)

Appendix A Schedule of Procedures – Extended Treatment Period

Study Period		Treatment Period																Post-Treatment Follow-up		
Study Week		Wk 54 & 56	Wk 58	Wk 60 & 62	Mo 15 Wk 64	Wk 66 & 68	Wk 70	Wk 72 & 74	Mo 18 Wk 76	Wk 78 & 80	Wk 82	Wk 84, 86, & 88	Mo 21 Wk 90	Wk 92 & 94	Wk 96	Wk 98, 100 & 102	Mo 24 Wk 104	Wk 106 & 108	Wk 110	Mo 27 Wk 117
Study Day		372 & 386	400	414 & 428	442	456 & 470	484	498 & 512	526	540 & 554	568	582, 596 & 610	624	638 & 652	666	680, 694 & 708	722	736 & 750	764	813
Visit Window+/- Days		2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	7	7
Outpatient Visit		X[f]	X[f]	X[f]	X	X[f]	X[f]	X[f]	X	X[f]	X[f]	X[f]	X	X[f]	X[f]	X[f]	X	X[f]	X[f]	X
Vital Signs (+ body weight)					X				X				X				X			X
Physical Examination									X								X			
12- lead ECG (triplicate)									X								X			
Urinalysis(including P/C ratio)			X		X		X		X		X		X		X		X		X	X
Blood Draw (Fasting)[b]	Chemistry Panel		X		X		X		X		X		X		X		X		X	X
	CBC with Differential[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Serum Lipid Panel				X				X				X				X			X
	Coagulation (aPTT, PT, INR)				X				X				X				X			
	Troponin I				X				X				X				X			X
	Plasma PK - ISIS 304801[c]								X								X			X
	Anti-ISIS 304801 Antibodies								X								X			X
	Serum Pregnancy Test[d]		X		X		X		X		X		X		X		X		X	X
Weekly Study Drug: SC Injection		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Diet/Alcohol Counseling[e]					X				X				X				X			
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Appendix A Schedule of Procedures – Extended Treatment Period *Continued*

Legend Text

a Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1 week and determined not to have met a stopping rule before dosing can continue. If there is no reportable platelet count within 14 days of the last platelet count, the Investigator will contact the patient to hold dosing until a new platelet count is obtained and reviewed. All platelet count results will be promptly reviewed by the Investigator to ensure that the count has not met the stopping rule and to determine whether the rate of decline is suggestive that the patient could be approaching the dose pause rule of 75,000/mm^3. Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor

b Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours. During treatment period urine and blood samples will be collected prior to Study Drug administration.

c Abbreviated PK collection (see Appendix C)

d Females of childbearing potential only

e To reinforce compliance to the diet and alcohol restrictions

f Assessments and procedures to be conducted by either a home healthcare nurse, or the Study Center as arranged by the Study Center personnel

Appendix B List of Laboratory Analytes

Appendix B List of Laboratory Analytes

Based on emerging data from this or future studies, additional tests not listed below may be performed on stored samples to better characterize the profile of volanesorsen or other similar oligonucleotides.

Clinical Chemistry Panel

- Sodium
- Potassium
- Chloride
- Bicarbonate
- Total protein
- Albumin
- Calcium
- Magnesium
- Phosphorus
- Glucose
- BUN
- Creatinine
- Uric Acid
- Total bilirubin
- Direct (conjugated) bilirubin
- Indirect (unconjugated) bilirubin
- ALT
- AST
- Alkaline phosphatase

Screening Tests (Group 3)

- Hepatitis B surface antigen
- Hepatitis C antibody
- HIV antibody
- FSH (women only)
- Serum βhCG (women only)

Coagulation

- aPTT (sec)
- PT (sec)
- INR

Lipid Panel

- Total Cholesterol
- LDL-C
- HDL-C
- Triglycerides
- Non-HDL-C
- VLDL-C
- apoA-1
- apoB
- apoC-III

Hematology

- Red blood cells
- Hemoglobin
- Hematocrit
- MCV, MCH, MCHC
- Platelets
- White blood cells
- WBC Differential (% and absolute)
  - Neutrophils
  - Eosinophils
  - Basophils
  - Lymphocytes
  - Monocytes

Pharmacokinetics[1] & Immunogenicity

- Volanesorsen levels in plasma
- Anti-volanesorsen antibodies in plasma

Other Assessments

- hsCRP
- Sedimentation Rate
- C5a, Bb
- Troponin I[2]
- CK-MB[2]
- Platelet Bound Autoantibodies[3]
- De-lipidated free glycerol
- HbA1c, FPG

Urinalysis

- Color
- Appearance
- Specific gravity
- pH
- Protein
- Blood
- Ketones
- Urobilinogen
- Glucose
- Bilirubin
- Leukocyte esterase
- Nitrate
- Microscopic examination[4]

Additional Measures for Expanded Urinalysis

- Total protein (quantitative)
- Microalbumin
- β2-microglobulin

1 Plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, IM testing (or possibly for purposes of IM assay development and/or validation), or to assess other actions of volanesorsen with plasma constituents

2 All abnormal troponin samples will be rerun at the central laboratory and also analyzed for CK-MB

3 May be done

4 Will be performed on abnormal findings unless otherwise specified

Appendix C Pharmacokinetic Sampling Schedule

Appendix C Pharmacokinetic Sampling Schedule

Blood samples for the determination of plasma volanesorsen concentrations will be collected prior to dosing, and at various times throughout the dosing and post-treatment follow-up period as noted in the tables below.

PK Sampling Schedule (All Patients except PK Subgroup)

Week	**Wk 1**	**Wk 4**	**Wk 8**	**Wk 13**	**Wk 26**	**Wk 38**	**Wk 52**	**Wk 65#**
Study Day	**D1**	**D22**	**D50**	**D85**	**D176**	**D260**	**D358**	**D449**
Visit Window +/- Days	0	2	2	2	2	3	2	7
Time Point	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime

Week 65 PK collection will be omitted for patients continuing to receive volanesorsen beyond Week 52

PK Sampling Schedule (PK Subgroup only*)

Week	**Wk 1**	**Wk 1**	**Wk 4**	**Wk 8**	**Wk 13**	**Wk 26**	**Wk 38**	**Wk 52**	**Wk 65#**
Study Day	**D1**	**D2**	**D22**	**D50**	**D85**	**D176**	**D260**	**D358**	**D449**
Visit Window +/- Days	0	0	2	2	2	2	3	2	7
Time Point	Pre-dose, 1, 2, 3, 4, 6, 8, and 12 hrs post-dose	24 hrs post-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime

* Patients at selected sites will be asked to participate in the extended 24-hour PK profile beginning on Study Day 1. Participation is optional

Week 65 PK collection will be omitted for patients continuing to receive volanesorsen beyond Week 52

PK Sampling Schedule (Extended Treatment Period)

Week	**Wk 76**	**Wk 104**	**Wk 117**
Study Day	**D526**	**D722**	**D813**
Visit Window +/- Days	2	2	7
Time Point	Pre-dose,	Pre-dose	Anytime

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

The following grading recommendations for adverse events relating to lab test abnormalities are based upon the **Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010**

Adverse Event	Mild	Moderate	Severe
Hematology			
aPTT prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage
Eosinophils increased†	650 – 1,500 cell/mm^3	1,501 - 5,000 cell/mm^3	>5,000 cell/mm^3
Fibrinogen decreased	<1.0 - 0.75 x LLN or <25% decrease from baseline	<0.75 - 0.5 x LLN or 25 - <50% decrease from baseline	<0.5 x LLN or ≥50% decrease from baseline
Hemoglobin decreased (Anemia)	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated
Hemoglobin increased	Increase in >0 - 2 g/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 g/dL above ULN or above baseline if baseline is above ULN	Increase in >4 g/dL above ULN or above baseline if baseline is above ULN
INR increased	>1 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation
Lymphocyte count decreased	<LLN - 800/mm^3; <LLN - 0.8 x 10^9/L	<800 - 500/mm^3; <0.8 - 0.5 x 10^9 /L	<500 /mm^3; <0.5 x 10^9 /L
Lymphocyte count increased	-	>4000/mm^3 - 20,000/mm^3	>20,000/mm^3
Neutrophil count decreased	<LLN - 1500/mm^3; <LLN - 1.5 x 10^9 /L	<1500 - 1000/mm^3; <1.5 - 1.0 x 10^9 /L	<1000/mm^3; <1.0 x 10^9 /L
Platelet count decreased	<LLN - 75,000/mm^3; <LLN - 75.0 x 10^9 /L	<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9 /L	<50,000/mm^3; <50.0 x 10^9 /L
White blood cell decreased	<LLN - 3000/mm^3; <LLN - 3.0 x 10^9 /L	<3000 - 2000/mm^3; <3.0 - 2.0 x 10^9 /L	<2000/mm^3; <2.0 x 10^9 /L
Chemistry			
Acidosis	pH <normal, but >=7.3	-	pH <7.3
Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Alkalosis	pH >normal, but ≤7.5	-	pH >7.5
Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 x ULN
Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

Adverse Event	Mild	Moderate	Severe
Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer
CD4 lymphocytes decreased	<LLN - 500/mm^3; <LLN - 0.5 x 10^9 /L	<500 - 200/mm^3; <0.5 - 0.2 x 10^9 /L	<200/mm^3; <0.2 x 10^9 /L
CPK increased*	>ULN - <6 ULN	6 - 10 x ULN	>10 x ULN
Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 x ULN
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 mg/dL; >3.1 mmol/L; Ionized calcium >1.6 mmol/L; hospitalization indicated
Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 mg/dL; >13.9 mmol/L; hospitalization indicated
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0; hospitalization indicated
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 mg/dL; >1.23 mmol/L
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 mmol/L; hospitalization indicated
Hyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 mg/dL; <1.75 mmol/L; Ionized calcium <0.9 mmol/L; hospitalization indicated
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 mg/dL; <3.0 mmol/L	<40 mg/dL (<2.2 mmol/L) AND requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions‡
Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 mmol/L; hospitalization indicated
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 mg/dL; <0.4 mmol/L
Hyponatremia	<LLN - 130 mmol/L	-	<130 mmol/L
Hypophosphatemia	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 mg/dL; <0.6 mmol/L
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

Adverse Event	Mild	Moderate	Severe
Urine			
Proteinuria Adults Children	1+ proteinuria; urinary protein <1.0 g/24 hrs -	2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs; Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Urinary protein ≥3.5 g/24 hrs; Urine P/C >1.9
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated

†Grading for this parameter is derived from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007

*Grading for this parameter is derived from the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0, Nov 2014

‡Modified for consistency with the ADA and Endocrine Society Guidelines (Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. Diabetes Care 2013;36:1384-95)

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Collaborator:
Akcea Therapeutics
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Cambridge, MA 02142

ISIS 304801-CS7

The APPROACH Open-Label Study

Volanesorsen (ISIS 304801)

An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol Amendment 6 - France – 16 September 2016

EudraCT No: 2015-003755-21

ISIS 304801-CS7

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An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol Amendment 6 - France – 16 September 2016

Protocol History:

Original Protocol:	28 August 2015
Protocol Amendment 1:	2 February 2016
Protocol Amendment 2:	22 April 2016
Protocol Amendment 3:	9 May 2016
Protocol Amendment 4:	6 June 2016
Protocol Amendment 5:	19 August 2016

Sponsor:

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[redacted]

[redacted] MD, MBA

[redacted]

Ionis Protocol Number: ISIS 304801-CS7

Protocol Amendment 6 - France

EudraCT No: 2015-003755-21

Clinical Phase: 3

The APPROACH Open-Label Study

Volanesorsen (ISIS 304801)

An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

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[redacted]
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Carlsbad, CA 92010
Phone: [redacted]

Collaborator: Akcea Therapeutics
55 Cambridge Parkway, Suite 100
Cambridge, MA 02142

Date: 16 September 2016

Confidentiality Statement

This document contains confidential information of Ionis Pharmaceuticals, Inc., that must not be disclosed to anyone other than the recipient study staff and members of the independent ethics committee, institutional review board, or authorized regulatory agencies. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc.

Protocol Signature Page

Protocol Number:	ISIS 304801-CS7
Protocol Title:	An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Amendment:	Amendment 6 - France
Date:	16 September 2016

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)", dated 16 September 2016, and agree to conduct the study as described herein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice (E6).

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc.

Investigator's Signature

Investigator's Name *(please print)* Date (DD Month YYYY)

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PROTOCOL AMENDMENT

Protocol Number:	ISIS 304801-CS7
Protocol Title:	An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Amendment Number:	6 - France
Amendment Date:	16 September 2016

The purpose of this protocol amendment is to incorporate changes requested by ANSM as part of the conditional approval of the study, dated 7 September 2016. As such, the following modifications to Protocol ISIS 304801-CS7 Amendment 5 dated 19 August 2016 have been made:

1. In order to reduce the unlikely but potential increased risk of pancreatitis during the period of corticosteroid therapy, triglyceride levels will be monitored weekly during corticosteroid treatment and the laboratory alert will be changed from 2,000 to 500 mg/dL during this period.
2. To increase the post-treatment follow-up period from 13 weeks to 26 weeks or longer, if needed, until apoC-III levels return to baseline values.

In addition, language was added to indicate that after completion of the Week 52 visit assessments, patients will enter the at least 26-week post-treatment evaluation period or will participate in an expanded access program pending approval by the IRBs/IEC, and the appropriate regulatory authorities.

Minor changes (not included in the list of changes below) have been made throughout the protocol to correct errors and/or to improve the overall clarity of the original protocol but these changes do not impact subject safety, exposure, or the overall study design.

The following table provides a summary list of major changes to the protocol:

Protocol Section	Description of Change	Rationale
Protocol Synopsis: Study Design Protocol Synopsis: Study Visit Schedule and Procedures 3.1 Study Design	**Was:** Following the Week 52 visit, patients will enter a 13-week post-treatment evaluation period. **Is:** Following the Week 52 visit, patients will enter an at least 26-week post-treatment evaluation period or will participate in an expanded access program pending approval by the IRBs/IEC, and the appropriate regulatory authorities.	To follow guidance provided by the ANSM to extend the post-treatment follow-up period until apoC-III levels return to baseline values To provide an expanded access program as an option for patients that may be benefiting from active drug treatment
Protocol Synopsis: Study Population 5.1 Inclusion Criteria	**Was:** 4. Able and willing to participate in a 65-week study **Is:** 4. Able and willing to participate in a 78-week study	To follow guidance provided by the ANSM to extend the post-treatment follow-up period until apoC-III levels return to baseline values

<table>
<tr><th>Protocol Section</th><th>Description of Change</th><th>Rationale</th></tr>
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<tr><td colspan="2">Outpatient Visit</td><td>X[l]</td><td>X[l]</td><td>X</td></tr>
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Protocol Section	Description of Change	Rationale
3.4.4 Post-Treatment 6.1.5 Post-Treatment Period	**Was:** After completion of the Week-52 visit assessments, patients will enter the 13-week post-treatment evaluation period. This period consists of 4 Study Center visits on Weeks 54, 56, and 58 (which may be conducted by a home healthcare nurse), and Week 65 as outlined in the Schedule of Procedures in Appendix A. **Is:** After completion of the Week 52 visit assessments, patients will enter the at least 26-week post-treatment evaluation period or will participate in an expanded access program pending approval by the IRBs/IEC, and the appropriate regulatory authorities. The 26-week period consists of at least 6 Study Center visits on Weeks 54, 56, 58, 65, 71, and 78 (Weeks 54, 56, 58, and 71 may be conducted by a home healthcare nurse), as outlined in the Schedule of Procedures in Appendix A.	To follow guidance provided by the ANSM to extend the post-treatment follow-up period until apoC-III levels return to baseline values To provide an expanded access program as an option for patients that may be benefiting from active drug treatment
For consistency with the above changes, Week 78 was added to the following sections: 6.2.4 ECG 6.2.6 Quality of Life Assessments 6.2.8 Diet Monitoring 8.8.1 Follow-up Visits for Early Termination from Treatment Period 8.8.2 Follow-up Visits for Early Termination from Post-Treatment Follow-up Period 8.10.2 Concomitant Procedures 9.4.1 Serious Adverse Events 9.4.2 Non-Serious Adverse Events Appendix C Pharmacokinetic Sampling Schedule		
8.6.3 Stopping Rules for Platelet Count Results Table 2 Actions in Patients with Low Platelet Count	**Was:** Administration of steroids is recommended for patients whose platelet count is less than 25,000/mm^3. Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (**note:** may require continuation with oral steroids after methylprednisolone). **Is:** Administration of steroids is recommended for patients whose platelet count is less than 25,000/mm^3. Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (**note:** may require continuation with oral steroids after methylprednisolone). In order to reduce the unlikely but potential increased risk of pancreatitis during the period of corticosteroid therapy, triglyceride levels will be monitored weekly during corticosteroid treatment and the laboratory alert will be changed from an increase of 2,000 to 500 mg/dL during that period.	To follow guidance provided by the ANSM to clarify the additional patient safety regarding monitoring of triglyceride levels

PROTOCOL SYNOPSIS

Protocol Title	An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Study Phase	3
Indication	Familial Chylomicronemia Syndrome
Study Objectives	To evaluate the safety and efficacy of dosing and extended dosing with volanesorsen (volanesorsen sodium 300 mg) in patients with FCS
Study Design	This is a multi-center open-label study of: Group 1: ISIS 304801-CS6 (index study) roll over FCS patients Group 2: ISIS 304801-CS16 (index study) roll over FCS patients Group 3: FCS patients who did not participate in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies All patients will receive volanesorsen 300 mg once per week for 52 weeks. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period. Following the Week 52 visit, patients will enter an at least 26-week post-treatment evaluation period or will participate in an expanded access program pending approval by the IRBs/IEC, and the appropriate regulatory authorities.
Number of Patients	Up to approximately 70 patients dosed
Study Population	<u>Inclusion Criteria:</u> 1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law 2. Age ≥ 18 years at time of informed consent 3. Groups 1 and 2: Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement. Groups 2 and 3: Patients must also meet the following criteria in order to enter into the open-label study: a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L) b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) by documentation of the following: • Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1) c. Group 2: Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 index study Group 3: Fasting TG ≥ 750 mg/dL at Screening for this open-label study 4. Able and willing to participate in a 78-week study

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	Inclusion Criteria: *Continued* 5. Satisfy 1 of the following: a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved), abstinent*, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration b. Males: Surgically sterile, abstinent* or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration * Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception Exclusion Criteria 1. Diabetes mellitus with any of the following: a. Newly diagnosed within 12 weeks of screening* b. HbA1c ≥ 9.0% at Screening* c. Recent change in anti-diabetic pharmacotherapy (change in dosage or addition of new medication within 12 weeks of screening* [with the exception of ± 10 units of insulin]) d. Anticipated need to change dose or type of medication during the treatment period of the Study (with the exception of ± 10 units of insulin) e. Current use of GLP-1 agonists 2. Severe hypertriglyceridemia other than due to familial chylomicronemia syndrome 3. Active pancreatitis within 4 weeks prior to screening* 4. History within 6 months of screening* of acute or unstable cardiac ischemia (myocardial infarction, acute coronary syndrome, new onset angina), stroke, transient ischemic attack or unstable congestive cardiac failure requiring a change in medication or major surgery within 3 months of screening*

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	Exclusion Criteria *Continued* 5. Any of the following laboratory values at Screening* a. Hepatic: • Total bilirubin > upper limit of normal (ULN), unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL • ALT > 2.0 x ULN • AST > 2.0 x ULN b. Renal: • Persistently positive (2 out of 3 consecutive tests ≥ 1+) for protein on urine dipstick. In the event of a positive test eligibility may be confirmed by a quantitative total urine protein measurement of < 500 mg/24 hrs • Persistently positive (2 out of 3 consecutive tests ≥ trace positive) for blood on urine dipstick. In the event of a positive test eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field • Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault < 50 mL/min (MDRD or CKD-EPI formulas can be used instead of Cockcroft-Gault for estimation of GFR in patients with low body weight after discussion with Sponsor Medical Monitor) c. Cardiac Troponin I > ULN at Screening* d. LDL-C > 130 mg/dL at Screening* e. Any other laboratory abnormalities which, in the opinion of the Investigator or the Sponsor, would make the patient unsuitable for inclusion 6. Uncontrolled hypertension (BP > 160/100 mm Hg) 7. History of thrombocytopenia (platelet count < 100,000/mm^3) or bleeding diathesis or coagulopathy or clinically-significant abnormality in coagulation parameters at Screening* 8. History of heart failure with NYHA greater than Class II 9. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1 10. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B 11. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated 12. Treatment with another investigational drug, biological agent, or device within 1-month of screening*, or 5 half-lives of investigational agent, whichever is longer 13. Unwilling to comply with lifestyle requirements (Section 6.3)

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	Exclusion Criteria *Continued* 14. Use of any of the following: a. Statins, omega-3 fatty acids (prescription and OTC), or fibrates unless on a stable dose for at least 3 months prior to screening* and dose and regimen expected to remain constant during the treatment period. Patients taking OTC omega-3 fatty acids should make every effort to remain on the same brand throughout the study b. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to screening* c. Systemic corticosteroids or anabolic steroids within 6 weeks prior to screening* unless approved by the Sponsor Medical Monitor d. Atypical antipsychotic medications (e.g., olanzapine and clozapine) unless on a stable dose for at least 3 months prior to screening* and dose and regimen expected to remain stable throughout the study e. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to screening* and dose and regimen expected to remain constant during the treatment period f. Glybera gene therapy within 2 years prior to screening* g. Oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, and apixaban) unless on a stable dose for at least 4 weeks prior to screening* and regular clinical monitoring is performed h. Tamoxifen, estrogens or progestins unless on a stable dose for at least 4 months prior to screening* and dose and regimen expected to remain constant during the treatment period i. Plasma apheresis within 4 weeks prior to screening* or planned during the study j. Prior exposure to ISIS 304801 k. Any other medication unless stable at least 4 weeks prior to screening* (Occasional or intermittent use of over-the-counter medications will be allowed at Investigator's discretion) 15. Blood donation of 50 to 499 mL within 30 days of screening* or of > 499 mL within 60 days of screening* 16. Known hypersensitivity to any of the excipients of the Study Drug (ISIS 304801 or placebo) 17. Have any other conditions, including new or worsening of existing condition, which, in the opinion of the Investigator or the Sponsor would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the study *(Group 3) or Qualification (Groups 1 and 2)
Treatment Group	Volanesorsen 300 mg once per week
Study Drug Administration	Volanesorsen will be administered as subcutaneous (SC) injections.
Dose Adjustments	Dose adjustments, including dose interruptions and/or decreasing the dose frequency will be allowed for safety or tolerability after consultation with the Sponsor Medical Monitor.

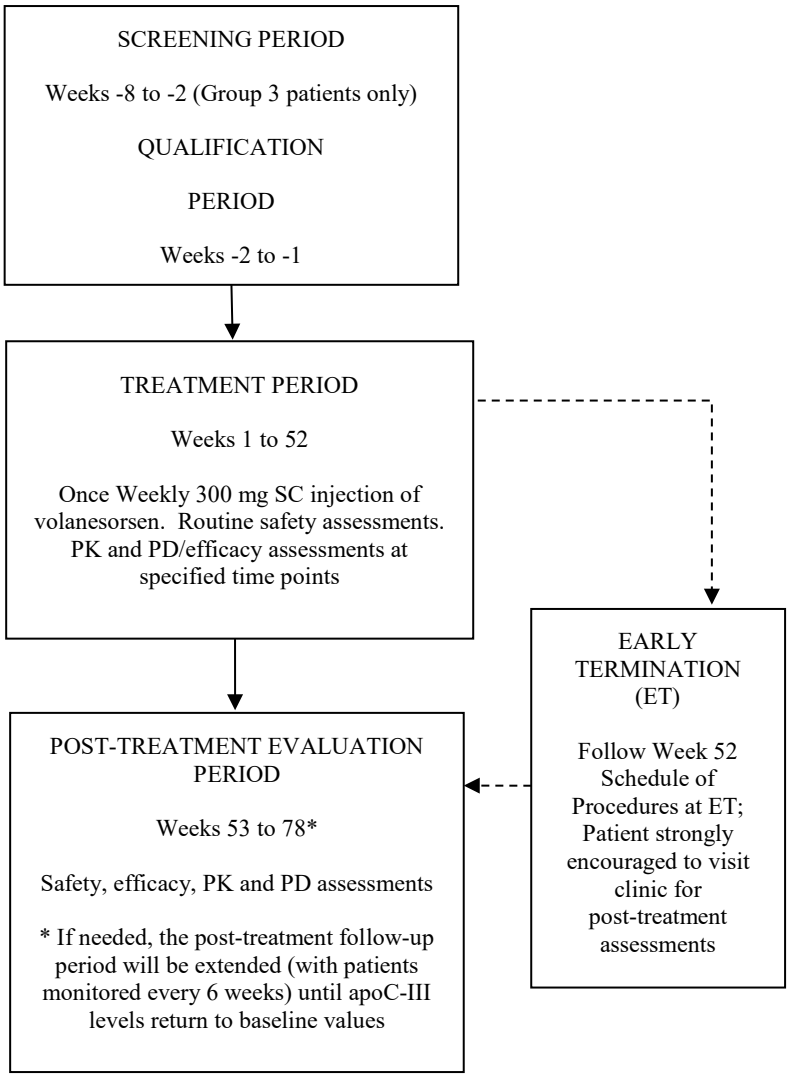
PROTOCOL SYNOPSIS *Continued*

Rationale for Dose and Schedule Selection	The dose of 300 mg once weekly was chosen for the double-blinded placebo-controlled Phase 3 index studies (ISIS 304801-CS6 and ISIS 304801-CS16) based on the pharmacodynamic and safety analysis of the Phase 2 studies (Section 2.4) which included a subset of patients with FCS. The same dose of 300 mg once weekly will be used in this open-label study of FCS patients.
Study Visit Schedule and Procedures	The study for an individual patient will generally consist of the following periods: • Group 1 and 2 patients (participated in ISIS 304801-CS6 or ISIS 304801-CS16 index study): A qualification period of up to 2 weeks (unless approved by the Sponsor). Please refer to Section 4.1 and Appendix A • Group 3 patients (did not participate in an index study): An up to 8-week screening and qualification period, including a diet stabilization period of at least 6 weeks (screening and diet stabilization period may be reduced, per Sponsor approval, if the patient is following a diet for optimal control of TGs and disease management prior to screening). Please refer to Section 6.1.2 and Appendix A • All patients: o A 52-week treatment period during which volanesorsen will be administered as a once weekly SC injection o An at least 26-week post-treatment evaluation period The patients, Investigators, study staff, and the Sponsor will remain blinded to lipid data through the last patient's Week 13 visit of the open-label study or until results from the database locks for the ISIS 304801-CS6 and ISIS 304801-CS16 index studies becomes available, whichever comes first. Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), adverse events (AE), concomitant medication/procedure information, lipid panel, volanesorsen plasma concentrations, immunogenicity (IM) testing, liver/spleen magnetic resonance imaging (MRI), ECGs, echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Dietary counseling will be repeated at intervals throughout the treatment and follow-up period and a daily food/drink diary will be completed for the week prior to each quarterly visit by each patient. Following the Week 52 visit, patients will enter an at least 26-week post-treatment evaluation period or will participate in an expanded access program pending approval by the IRBs/IEC, and the appropriate regulatory authorities.

PROTOCOL SYNOPSIS *Continued*

Safety and Tolerability Evaluations	Overall safety and tolerability of volanesorsen will be assessed by determining the incidence and severity of adverse and serious adverse events (including independently adjudicated events of acute pancreatitis and MACE), withdrawals due to adverse events, and changes in laboratory and other safety parameters.
Planned Analyses	Safety Endpoints: • Adverse events including adjudicated events of acute pancreatitis and MACE • Vital signs and weight • Physical examinations • Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis) • Echocardiography • Electrocardiograms (ECGs) • Use of concomitant medications • MRIs Efficacy Endpoints: • Percent change and absolute change from baseline in fasting TG • Frequency and severity of patient reported abdominal pain during the treatment period • Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-high-density lipoprotein-cholesterol (non-HDL-C), apolipoprotein B [apoB], high-density lipoprotein-cholesterol (HDL-C), apolipoprotein A-1 [apoA-1], very-low-density lipoprotein-cholesterol (VLDL-C), and LDL-C • Percent change from baseline in fasting total apolipoprotein C-III (apoC-III) • Quality of Life questionnaires (EQ-5D, SF-36) • Adjudicated acute pancreatitis event rate • Other symptoms: eruptive xanthoma, lipemia retinalis
Pharmacokinetic Evaluations	Plasma samples will be taken from all patients for the measurement of volanesorsen as follows: trough levels (pre-dose) throughout treatment and post-treatment levels during the post-treatment follow-up period. In a subset of patients, more frequent assessment of plasma concentrations of volanesorsen will be performed to determine volanesorsen pharmacokinetic parameters. Plasma sample collection time points are detailed in Appendix A and Appendix C.
Statistical Considerations	No sample size calculations were performed as this is an open-label study.
Sponsor	Ionis Pharmaceuticals, Inc.
Collaborator	Akcea Therapeutics

STUDY DESIGN AND TREATMENT SCHEMA



STUDY GLOSSARY

Abbreviation/Acronym	Definition
ADA	anti-drug antibody
AE	adverse Event
ALP	alkaline Phosphatase
ALT	alanine Aminotransferase
ANA	antinuclear Antibody
apoA-1	apolipoprotein A-1
apoB	apolipoprotein B
apoC-III	apolipoprotein C-III
apoE	apolipoprotein E
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
CBC	complete blood count
C_{max}	maximum observed drug concentration
CRF	case report form
DNA	deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
ET	early termination
FAS	full analysis set
FCS	Familial Chylomicronemia Syndrome
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
GPIHBP1	Glycosylphosphatidylinositol-anchored HDL-binding Protein 1
HAPI	Heritability and Phenotype Intervention
HbA1c	Glycated Hemoglobin
HDL	High-Density Lipoprotein
HDL-C	High-Density Lipoprotein-Cholesterol
hsCRP	High-sensitivity C-reactive protein
ICH	International Conference on Harmonization
IDL	Intermediate density lipoprotein
IEC	Independent Ethics Committee
IM	immunogenicity
Index Studies	ISIS 304801-CS6 and ISIS 304801-CS16

STUDY GLOSSARY *Continued*

INR	International Normalized Ratio
IRB	Institutional Review Board
IXRS	Interactive Voice/Web-Response System
LDL	Low-Density Lipoprotein
LDL-C	Low-Density Lipoprotein-Cholesterol
LMF1	Lipase Maturation Factor 1
LPL	Lipoprotein Lipase
MACE	Major Acute Cardiovascular Event
MOE	2′-*O*-(2-methoxyethyl)
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NCS	not clinically-significant
NOAEL	No-Observed-Adverse-Effect Level
non-HDL-C	Non-High-Density Lipoprotein-Cholesterol
OTC	over the counter
PFS	prefilled syringe
PD	pharmacodynamic
PK	pharmacokinetic
PPS	per protocol set
PT	prothrombin time
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SUSAR	suspected unexpected serious adverse reaction
T2DM	type 2 diabetes mellitus
T_{max}	time to maximal concentration
TG	triglycerides
Treatment-emergent	occurring after first dose of Study Drug
TRL	Triglyceride-Rich Lipoproteins
ULN	upper limit of normal
VLDL	Very-Low-Density Lipoprotein
VLDL-C	Very-Low-Density Lipoprotein-Cholesterol
VLDL-TG	Lipoprotein-Triglyceride
WMA	World Medical Association

1. OBJECTIVES

The objective of the study is to evaluate the safety and efficacy of dosing and extended dosing with volanesorsen in patients with familial chylomicronemia syndrome.

2. BACKGROUND AND RATIONALE

2.1 Overview of Disease

Familial Chylomicronemia Syndrome (FCS) is an inherited disease characterized by severe hypertriglyceridemia and chylomicronemia, and risk or history of pancreatitis. It is a rare autosomal recessive disease that can be diagnosed either in childhood or adulthood.

Fasting plasma triglyceride (TG) levels in FCS patients are typically 10-fold to 100-fold above normal (1,500 to 15,000 mg/dL), despite extreme dietary fat restriction (20 g or approximately 15-20% of daily calorie intake) (Brunzell 1999-2011). Patients with FCS often present in infancy or childhood with frequent and severe abdominal pain, repetitive colicky pain, repeated episodes of potentially fatal acute pancreatitis, and failure to thrive (Brunzell 1999-2011; Tremblay et al. 2011). Physical examination frequently reveals eruptive xanthomas, lipemia retinalis and hepatosplenomegaly, and plasma from patients appears lactescent, interfering with determination of other laboratory parameters (Tremblay et al. 2011).

Patients with fasting triglyceride levels > 10 mmol/L probably have a component of chylomicronemia. Clinical diagnosis would include evidence of clinical features of chylomicronemia syndrome and secondary causes such as uncontrolled type 1 or type 2 diabetes mellitus (T2DM), hypothyroidism, poor diet, alcohol use, nephrotic syndrome or use of associated medications should be ruled out. The diagnosis of FCS may be made more specifically by genotyping or confirmation of very low or absent lipoprotein lipase (LPL) enzyme activity in post heparin plasma (Brunzell 1999-2011).

Patients with FCS carry a heavy burden of medical complications, the most serious, as described above, being an extreme risk of recurrent and potentially fatal pancreatitis. Due to the recurrent episodes of acute pancreatitis, these patients may also develop chronic pancreatitis and signs of exocrine or endocrine pancreatic insufficiency, including diabetes mellitus (Gaudet et al. 2013). While the pathophysiology underlying chylomicron-related pancreatitis has not been completely elucidated, 1 hypothesis is that large chylomicrons lodged in pancreatic capillaries are exposed to pancreatic lipase, with the subsequent release of free fatty acids through the hydrolysis of chylomicron-associated TGs. High concentrations of free fatty acids are thought to damage pancreatic cells leading to emergent pancreatitis (Yang et al. 2009; Berglund et al. 2012).

The etiology of extreme hypertriglyceridemia in FCS is considered to be ineffective triglyceride clearance, due to an extremely low level of LPL activity. LPL normally functions to hydrolyze triglycerides (TG) in chylomicrons along the luminal surface of capillaries, mainly in heart, skeletal muscle, and adipose tissue, promoting triglyceride clearance from the circulation. LPL is regulated by a number of key genes, and loss-of-function mutations in one of these genes, or the LPL gene itself, results in FCS (Surendran et al. 2012). In addition to loss of function mutations, null mutations, and nonsense mutations in the LPL gene, other genes currently identified in FCS patients, and known to directly influence LPL activity include: apolipoprotein C-II (APOC2) a cofactor for LPL (Schuster et al. 2011); apolipoprotein A-V

(APOA5) an enhancer of LPL activity (Schaap et al. 2004); lipase maturation Factor 1 (LMF1), a transmembrane protein involved in LPL maturation (Doolittle et al. 2009); glycosylphosphatidylinositol-anchored HDL-binding protein 1 (GPIHBP1), a capillary endothelial cell protein that provides a platform for LPL-mediated processing of chylomicrons (Beigneux et al. 2007).

2.2 Therapeutic Rationale

Apolipoprotein C-III (ApoC-III), a key regulator of plasma triglyceride levels, is a 79 amino acid glycoprotein synthesized principally in the liver (Ooi et al. 2008; Figure 1). ApoC-III is a major regulator of lipoprotein metabolism and plays a pivotal role in regulating plasma TG levels (Chan et al. 2008). It is a component of triglyceride-rich lipoproteins (TRLs) and a potent inhibitor of LPL (Lemieux et al. 2003). At higher concentrations apoC-III also inhibits hepatic lipase activity (Kinnunen and Ehnolm 1976), an enzyme which plays an important role in the conversion of dense very-low-density lipoprotein (VLDL) to intermediate density lipoprotein (IDL) and to LDL (Mendivil et al. 2010), as well as in the remodeling of HDL (Brown et al. 2010). In addition, increased apoC-III content adversely affects apoE-mediated hepatic uptake of TG-rich remnants (Mann et al. 1997). Thus, elevated plasma apoC-III levels are associated with impaired hydrolysis and retarded clearance of TG-rich particles, resulting in the accumulation of lipoprotein-triglyceride (VLDL-TG) and chylomicrons in plasma and the development of hypertriglyceridemia (Ito et al. 1990).

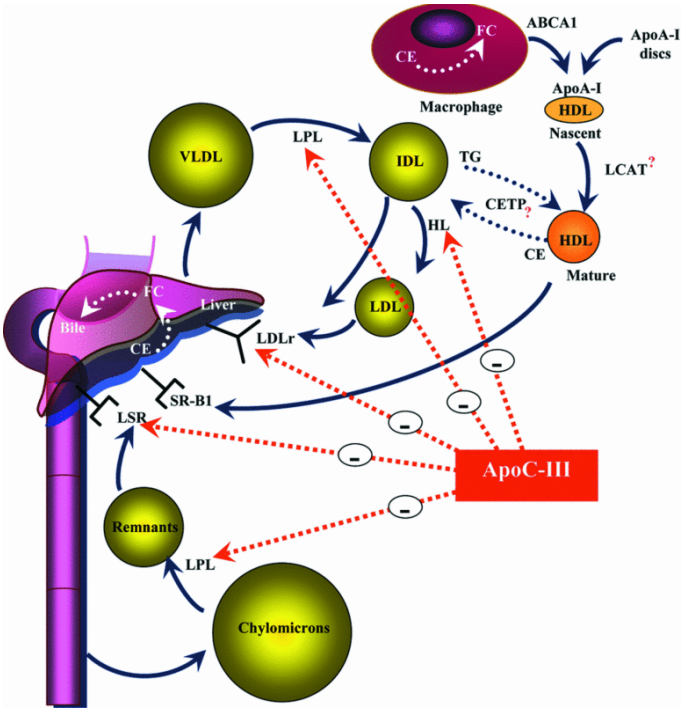


Figure 1 ApoC-III Regulates Lipoprotein Metabolism by Multiple Mechanisms

From Ooi et al. 2008; ABCA1 = ATP-binding cassette A1, apo = apolipoprotein, CE = cholesterol ester, CETP = cholesterol ester transfer protein, FC = free cholesterol, HDL = high-density lipoprotein, HL = hepatic lipase, IDL = intermediate-density lipoprotein, LCAT = lecithin cholesterol acyltransferase, LDL = low-density lipoprotein, LDLr = LDL receptor, LPL = lipoprotein lipase, LSR = lipolysis-stimulated receptor, SR-B1 = scavenger receptor B-1, TG = triglyceride, VLDL = very low-density lipoprotein.

Mechanistically, FCS is primarily a consequence of ineffective clearance of TRL. ApoC-III is a prominent component of TRL (e.g., VLDL and chylomicrons). In addition to its role in inhibiting LPL, apoC-III inhibits TRL remnant (TG-depleted remnant lipoprotein) uptake by hepatic lipoprotein receptors by steric inhibition of the interaction of apoE with these receptors.

Human genetic data have demonstrated positive phenotypic associations with loss (e.g., null or nonsense mutations) and negative effects with gain of function mutations (Atzmon et al. 2006; Pollin et al. 2008; Petersen et al. 2010). A novel nonsense mutation in the apoC-III gene was identified in the heritability and phenotype intervention (HAPI) heart study in Old Order Amish that results in lower plasma apoC-III and TG levels and lower LDL-C, increased HDL-C and reduced atherosclerosis (Pollin et al. 2008). In another study involving a group of 214 Ashkenazi Jews of advanced age (had passed or nearly reached 100 years of age), genotype analysis revealed a polymorphism in the apoC-III gene (APOC3-641CC genotype) with a clear pattern of age-dependent frequency that was associated with significantly lower levels of apoC-III protein, a favorable lipoprotein profile and increased longevity (Atzmon et al. 2006). In contrast to the Amish and Ashkenazi apoC-III polymorphisms associated with lower plasma TG, apoC-III polymorphisms associated with higher plasma TG have also been recently described (Petersen et al. 2010). In a cohort of lean (mean body mass index [BMI] = 24.7 ± 3.6 kg/m^2) Asian Indians, carriers of apoC-III variant alleles (C-482T, T-455C, or both) were noted to have significantly higher plasma apoC-III and TG levels, and decreased ability to clear postprandial plasma TG from the circulation. Taken together, the available data strongly support the development of a therapy that reduces plasma apoC-III levels in order to reduce the very high circulating triglyceride and chylomicron levels that are accompanied by increasing risk for acute pancreatitis.

Given the profound reductions in TGs observed with volanesorsen treatment in FCS patients who have no detectable LPL activity (See Section 2.3.4), and the mechanistic data available to date on apoC-III function, potential mechanisms that explain how apoC-III inhibition results in triglyceride reduction in FCS patients include: (1) enhancing the very small residual amounts of LPL activity that these patients may have, below the limit of detection of the assay in many cases (2) potentially enhanced activity of other lipases also involved in the metabolism and breakdown of TGs, such as hepatic lipase or endothelial lipase (Kinnunen and Ehnolm 1976), and (3) apoC-III interaction with Apolipoprotein E (apoE), an important factor in liver reuptake of lipid particles by blocking apoE-mediated uptake of lipid particles in the liver (Breyer et al. 1999), and therefore, reducing apoC-III might enhance apoE-mediated uptake of lipid particles. Volanesorsen-mediated reduction of apoC-III could be contributing to one or all of these mechanisms resulting in the observed potent and sustained reductions in TG.

Through a novel apoC-III lowering mechanism of action, volanesorsen may provide the potential to manage triglyceride levels in FCS patients.

2.3 Volanesorsen

2.3.1 Mechanism of Action

Volanesorsen is a second-generation antisense oligonucleotide (ASO) drug targeted to human apoC-III. It is complementary to a region within the 3′ untranslated region of the apoC-III messenger ribonucleic acid (mRNA) and binds to the mRNA by Watson and Crick base pairing.

The hybridization (binding) of volanesorsen to the cognate mRNA, results in the RNase H1-mediated degradation of the apoC-III mRNA, thus preventing production of the apoC-III protein. Maximal antisense-mediated reduction of target mRNA levels is typically greater than 90% of control levels in sensitive tissues (Crooke and Bennett 1996; Zhang et al. 2010). Furthermore, reduction in target mRNA levels using this approach correlates directly with a subsequent reduction in target protein levels.

2.3.2 Chemistry

Chemically, volanesorsen is a synthetic oligomer of 20 nucleotides (i.e., a 20-mer) that are connected sequentially by phosphorothioate linkages. The nucleotide sequence of volanesorsen (Figure 2) is complementary to a 20-nucleotide stretch within the 3′ untranslated region of the apoC-III mRNA transcript at base position 489-508. Structurally, the oligonucleotide has 3 regions. Two (2) of them, the 5 nucleotides at the 5′ end and the 5 nucleotides at the 3′ end, are composed of 2′-*O*-(2-methoxyethyl) (MOE)-modified ribonucleotides. These MOE-modified nucleotides confer (1) increased affinity to the target mRNA (Altmann et al. 1996; McKay et al. 1999), (2) increased resistance to exonucleases and endonucleases (thereby increasing stability in tissue) (Geary et al. 2003), and (3) amelioration of some of the high dose toxicities thereby resulting in an improved safety profile compared to first generation antisense drugs containing phosphorothioate modified oligodeoxynucleotides (DNA) (Henry et al. 2000). The third region, the central portion of the oligonucleotide, is composed of 10 oligodeoxynucleotides. This chimeric design is called a MOE-Gapmer, and volanesorsen employs this chimeric structure to enable use of the RNase H1-mechanism for antisense activity. This is because while the 2′-MOE modification confers increased stability and affinity, it does not support RNase H1 catalysis of RNA hybridized to 2′-MOE-modified nucleotides (McKay et al. 1999). This is caused by conformational changes induced in the heteroduplex by 2′-alkoxy:RNA hybrids that are not recognized by RNase H1 enzymes (Inoue et al. 1987; Monia et al. 1993). By limiting the 2′-MOE modification to nucleotides flanking the phosphorothioate oligodeoxynucleotide core, the beneficial attributes of the 2′-MOE chemistry are preserved while also retaining RNase H1 recognition.

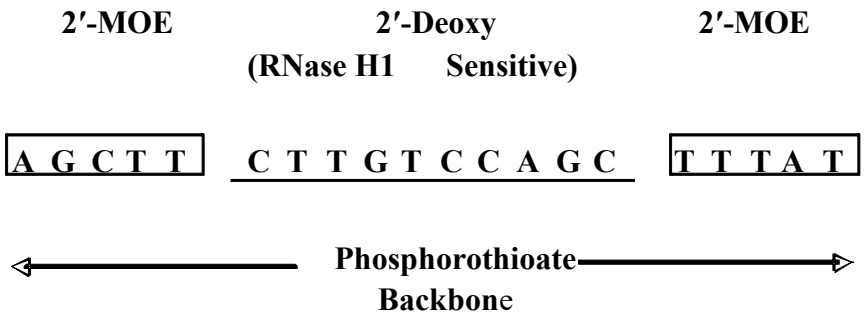


Figure 2 Design of Chimeric 2′-MOE Phosphorothioate Oligonucleotides (MOE-Gapmer). The sequence of volanesorsen is shown

2.3.3 Preclinical Experience

Inhibition of apoC-III using volanesorsen has been shown to potently reduce hepatic apoC-III mRNA as well as plasma apoC-III protein and TG in a dose- and time-dependent fashion in several species, including human apoC-III transgenic mice, and other rodent and monkey models. Treatment with volanesorsen also resulted in reduced VLDL and chylomicron TG and reduced postprandial TG in hypertriglyceridemic monkeys (Graham et al. 2013).

The pharmacokinetics (PK) and toxicity of volanesorsen have been assessed in mice, rats, and cynomolgus monkeys. General toxicity studies with volanesorsen for up to 39 weeks of treatment followed by up to a 20-week recovery period are complete. The preclinical toxicology program for volanesorsen consists of single dose safety pharmacology studies in the monkey (cardiovascular) and mouse (neurobehavioral and pulmonary assessment studies), *in vitro* and *in vivo* genetic toxicity assessment, repeat dose fertility and/or developmental reproductive toxicology studies in the mouse and rabbit and evaluation in the *in vitro* human Ether-á-go-go-related gene (hERG) assay.

Volanesorsen treatment-related findings in mice and monkeys were generally consistent with those expected for the 2′-MOE-class of ASOs. Treatment-related findings included effects consistent with drug accumulation in tissues in rodents and monkeys, species-dependent proinflammatory response in rodents and monkeys and complement activation and reductions in platelet counts in the monkey. In the mouse and monkey general toxicity studies, reduction of hepatic apoC-III mRNA (> 75%) was not associated with any findings that could be considered related to the pharmacologic inhibition of apoC-III for up to 39 weeks of treatment.

The long-term, chronic toxicology studies in rodents with volanesorsen produced a significant proinflammatory response that led to subsequent effects on the heart at high doses. The rodent species are most sensitive to the proinflammatory effects of antisense molecules. Importantly, these effects on the heart were not observed in the monkey chronic toxicity studies even at the highest doses tested where drug exposure was higher than that in rodents.

Because these changes were not observed in monkeys, the findings in the heart are considered to be rodent-specific and not relevant to humans. Nevertheless, such effects will be monitored by measurement of echocardiograms that will be included in this clinical study.

Volanesorsen caused no untoward effects in safety pharmacology studies (*in vitro* and *in vivo*) and was non-genotoxic (*in vitro* and *in vivo*). Volanesorsen had no effects on fertility or embryo/fetal development in the mouse or rabbit reproductive toxicity studies. In these studies, volanesorsen was detected in placental tissue but not in fetal tissue indicating that little, if any, drug was able to cross the placenta to reach the fetus. Reduction of apoC-III mRNA (64% in males and 47% in females) also did not affect fertility or cause untoward effects on embryo/fetal development in mice.

Detailed information concerning the preclinical studies conducted with volanesorsen can be found in the volanesorsen Investigator's Brochure.

2.3.4 Clinical Experience

Detailed information concerning the clinical studies conducted with volanesorsen can be found in the volanesorsen Investigator's Brochure. A summary is included below.

Volanesorsen has been evaluated in one Phase 1 study and two Phase 2 studies, all double blinded and placebo controlled. The total exposures comprise 99 patients and healthy volunteers administered volanesorsen from 50 to 400 mg subcutaneously up to 3 months (compared to 37 administered placebo).

All clinical trials of volanesorsen have shown large and clinically meaningful reductions in fasting plasma apoC-III and TG (~80% and 70%, respectively, mean reduction from baseline with 300 mg dose) with a very high degree of consistency of response between the different patient groups. This includes healthy volunteers, patients with moderate to severe hypertriglyceridemia not on background TG-lowering therapy, patients with moderate to severe hypertriglyceridemia on a background stable fibrate therapy (Gaudet et al. 2015), patients with FCS, and patients with T2DM.

In a Phase 2 study, 3 patients with FCS were treated with 300 mg/wk volanesorsen in an open-label fashion. These patients had a mean baseline fasting TG level of 1,844 mg/dL and all 3 patients achieved TG levels below or close to 500 mg/dL during the dosing period out to Day 92 (Figure 3). Two (2) of the FCS patients had an absolute reduction in fasting TG in excess of 1,500 mg/dL (Gaudet et al. 2014).

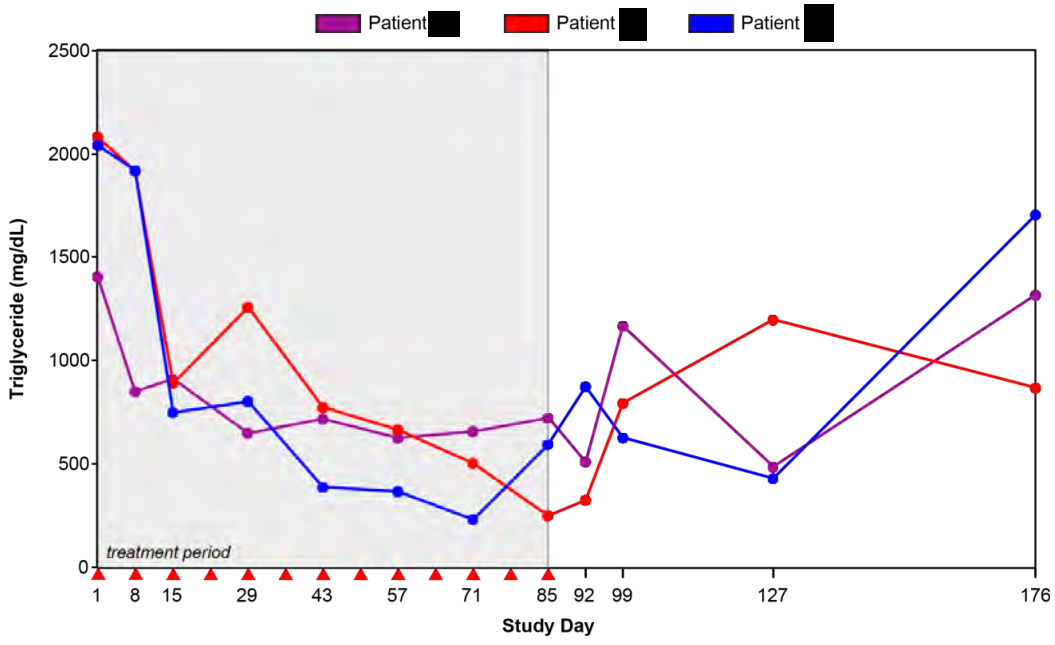


Figure 3 Fasting Triglycerides in Patients with FCS Treated with Volanesorsen

In clinical studies conducted to date volanesorsen has been well-tolerated and has shown a favorable safety profile. There has been no clinical or laboratory evidence of drug-drug interactions.

In the completed studies there have been no volanesorsen associated laboratory abnormalities suggestive of an effect on the renal (serum creatinine, proteinuria) or hepatic systems (alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin). In Phase 2 studies, there was a mild decrease of platelet count associated with volanesorsen administration that recovered in the post-treatment period and was not associated with platelet-related adverse events (AEs). In the blinded ongoing clinical trials of ISIS 304801, 2 patients of 142 dosed (as of February 29, 2016) had a decrease in platelet count to less than 50,000/mm^3 in the absence of major bleeding or clinically-relevant non-major bleeding and had Study Drug paused as per the monitoring and stopping rules for platelet counts (Section 8.6.3). Platelet counts recovered following suspension of dosing.

The most frequently observed AEs with volanesorsen were local reactions at the injection site. Local cutaneous reactions at the injection site defined as those events presenting as either pain, tenderness, erythema, pruritus or swelling occurring on the day of injection and persisting for at least 2 days were infrequent (~15% of injections), were almost always mild, resolved spontaneously, were non-progressive, and were not associated with systemic sequelae.

2.4 Rationale for Dose and Schedule of Administration

The dose and schedule selected for this study is 300 mg per week for 52 weeks. The dose of 300 mg per week is supported by both the cumulative nonclinical data available to date and the Phase 2 clinical data. In nonclinical studies, volanesorsen treatment-related effects in rodents and monkeys were consistent with drug accumulation in tissues and also include species-specific proinflammatory responses. In the monkey, the No-Observed-Adverse-Effect Level (NOAEL) was defined by the cumulative clinical pathology results and histopathology data which provide an adequate clinical margin. No nonclinical findings were considered to be related to the pharmacologic inhibition of apoC-III.

The safety data to date suggest that volanesorsen has been well-tolerated at dose levels up to 300 mg in patients with high triglycerides (including type 2 diabetes patients and administration in combination with fibrates and statins) with the most common AEs being local to the injection site and predominantly mild. A pooled analysis of safety for the Phase 2 studies did not demonstrate any clear difference in safety or tolerability between the different doses tested (100 mg, 200 mg, and 300 mg per week for 13 weeks).

Analysis of the cohorts in which volanesorsen was studied at different doses demonstrates dose-dependent pharmacology with respect to pharmacodynamic (PD) effect on the target, apoC-III, with a clear difference in the TG-lowering effect between the different doses in the 100 mg to 300 mg dose range as compared to placebo.

In addition to the nonclinical and clinical experience of volanesorsen, the dose and schedule of administration is supported by the preclinical and clinical safety experience of several other 2′-MOE-modified ASOs that have been safely administered intravenously and subcutaneously in multiple clinical studies at doses up to 1000 mg and for treatment durations that exceed 24 months (Santos et al. 2015).

3. EXPERIMENTAL PLAN

3.1 Study Design

This is an open-label study of:

Group 1: ISIS 304801-CS6 (index study) roll over FCS patients

Group 2: ISIS 304801-CS16 (index study) roll over FCS patients

Group 3: FCS patients who did not participate in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies

Up to approximately 70 patients will receive 300 mg once weekly volanesorsen for 52 weeks.

Following the Week 52 visit, patients enter an at least 26-week post-treatment evaluation period or will participate in an expanded access program pending approval by the IRBs/IEC, and the appropriate regulatory authorities.

3.2 Number of Study Centers

This study will be conducted at multiple centers worldwide.

3.3 Number of Patients

Up to approximately 70 patients will be dosed.

3.4 Overall Study Duration and Follow-up

The Study will consist of the following periods:

3.4.1 Group 1 and 2 Patients (participated in ISIS 304801-CS6 or ISIS 304801–CS16 index study): Qualification

A period of up to 2 weeks (unless approved by the Sponsor) is given to complete qualification assessments outlined in the Schedule of Procedures. Please refer to Section 4.1 and Appendix A.

3.4.2 Group 3 Patients (did not participate in an index study): Screening/Qualification

An up to 8-week screening and qualification period, including a diet stabilization period of at least 6 weeks (screening and diet stabilization period may be reduced, per Sponsor approval, if the patient is following a diet for optimal control of TGs and disease management prior to screening. Please refer to Section 6.1.2 and Appendix A.

3.4.3 Treatment

The treatment period is 52 weeks. Eligible patients will report to the Study Center for assessments at specified intervals throughout the 52-week treatment period as detailed in the Schedule of Procedures (Appendix A). During the treatment period, volanesorsen is administered by SC injection once weekly.

3.4.4 Post-Treatment

The post-treatment evaluation period is at least 26 weeks and consists of at least 6 Study Center visits on Weeks 54, 56, 58, 65, 71, and 78 (Weeks 54, 56, 58, and 71 may be conducted by a home healthcare nurse).

3.5 End-of-Study

The End-of-Study is last patient, last visit.

3.6 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will review (as needed) safety, tolerability and efficacy data collected on volanesorsen during this study. Based on its ongoing assessment of the safety and tolerability of volanesorsen, the DSMB will provide recommendations to the Sponsor for modifying, stopping or continuing the study as planned. Details on the safety assessments, frequency of review and meeting schedules are outlined in the DSMB Charter and/or the statistical analysis plan (SAP).

4. PATIENT ENROLLMENT

4.1 Screening/Qualification

Before patients may be enrolled into the study, the Sponsor requires a copy of the Study Center's written independent ethics committee/institutional review board (IEC/IRB) approval of the protocol, informed consent form, and all other patient information.

Patients or their legally acceptable representatives must sign the consent form before any study-specific procedures or evaluations related to this open-label study are performed.

Groups 1 and 2 (Qualification): During the qualification period, the eligibility of the patient to enroll in the open-label study will be determined. Final assessments from the ISIS 304801-CS6 or ISIS 304801-CS16 studies may be used for qualification. A period of up to 2 weeks after completion of the ISIS 304801-CS6 or ISIS 304801-CS16 index studies (unless approved by the Sponsor) is given to complete qualification. Qualified patients will retain the unique patient identification number that was assigned to them during the ISIS 304801-CS6 or ISIS 304801-CS16 index studies. The patient identification number will be used to identify the patient throughout the extension trial and must be used on all study documentation related to that patient. The patient identification number must remain constant throughout the extension trial.

Group 3 (Screening and Qualification): At the time of consent, the patient will be considered enrolled into the study and will be assigned a unique screening number before any study procedures, including screening procedures, are performed. At the time of enrollment, patients will be assigned a unique patient identification number. This number will be used to identify the patient throughout the trial and must be used on all study documentation related to that patient. The screening number and patient identification number must remain constant throughout the entire trial. In the event the patient is re-consented and re-screened the patient must be given a new screening number. Screening numbers and patient identification numbers, once assigned, will not be re-used.

4.2 Enrollment

Patients will be enrolled into the treatment phase of the study after all Screening (Group3) and qualification assessments have been completed and after the Investigator has verified that they are eligible per criteria in Sections 5.1 and 5.2. No patient may begin treatment prior to enrollment.

Eligible patients will be enrolled using an Interactive Voice/Web-Response System (IXRS).

5. PATIENT ELIGIBILITY

To be eligible to participate in this study candidates must meet the following eligibility criteria within 2 weeks of Study Day 1, or at the time point specified in the individual eligibility criterion listed.

5.1 Inclusion Criteria

1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law

2. Age ≥ 18 years at time of informed consent

3. Groups 1 and 2: Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement.

   Groups 2 and 3: Patients must also meet the following criteria in order to enter into the open-label Study:

   a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L)

   b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) by documentation of the following:

      - Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1)

   c. Group 2: Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 index study
      Group 3: Fasting TG ≥ 750 mg/dL at Screening for this open-label study

4. Able and willing to participate in a 78-week study

5. Satisfy 1 of the following:

   a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative

medical cause and FSH levels in the postmenopausal range for the laboratory involved), abstinent*, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration.

b. Males: Surgically sterile, abstinent* or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration.

* Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception

5.2 Exclusion Criteria

1. Diabetes mellitus with any of the following:
   a. Newly diagnosed within 12 weeks of screening*
   b. HbA1c ≥ 9.0% at Screening*
   c. Recent change in anti-diabetic pharmacotherapy (change in dosage or addition of new medication within 12 weeks of screening* [with the exception of ± 10 units of insulin])
   d. Anticipated need to change dose or type of medication during the treatment period of the Study (with the exception of ± 10 units of insulin)
   e. Current use of GLP-1 agonists
2. Severe hypertriglyceridemia other than due to familial chylomicronemia syndrome
3. Active pancreatitis within 4 weeks prior to screening*
4. History within 6 months of screening* of acute or unstable cardiac ischemia (myocardial infarction, acute coronary syndrome, new onset angina), stroke, transient ischemic attack or unstable congestive cardiac failure requiring a change in medication or major surgery within 3 months of screening*
5. Any of the following laboratory values at Screening*
   a. Hepatic:
      - Total bilirubin > upper limit of normal (ULN), unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL
      - ALT > 2.0 x ULN

- AST > 2.0 x ULN

b. Renal:

- Persistently positive (2 out of 3 consecutive tests ≥ 1+) for protein on urine dipstick. In the event of a positive test eligibility may be confirmed by a quantitative total urine protein measurement of < 500 mg/24 hrs
- Persistently positive (2 out of 3 consecutive tests ≥ trace positive) for blood on urine dipstick. In the event of a positive test eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field
- Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault < 50 mL/min (MDRD or CKD-EPI formulas can be used instead of Cockcroft-Gault for estimation of GFR in patients with low body weight after discussion with Sponsor Medical Monitor)

c. Cardiac Troponin I > ULN at Screening*

d. LDL-C > 130 mg/dL at Screening*

e. Any other laboratory abnormalities which, in the opinion of the Investigator or the Sponsor, would make the patient unsuitable for inclusion

6. Uncontrolled hypertension (BP > 160/100 mm Hg)
7. History of thrombocytopenia (platelet count < 100,000/mm^3) or bleeding diathesis or coagulopathy or clinically-significant abnormality in coagulation parameters at Screening*
8. History of heart failure with NYHA greater than Class II
9. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1
10. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B
11. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated
12. Treatment with another investigational drug, biological agent, or device within 1-month of screening*, or 5 half-lives of investigational agent, whichever is longer
13. Unwilling to comply with lifestyle requirements (Section 6.3)
14. Use of any of the following:

a. Statins, omega-3 fatty acids (prescription and OTC), or fibrates unless on a stable dose for at least 3 months prior to screening* and dose and regimen expected to

remain constant during the treatment period. Patients taking OTC omega-3 fatty acids should make every effort to remain on the same brand throughout the study

b. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to screening*

c. Systemic corticosteroids or anabolic steroids within 6 weeks prior to screening* unless approved by the Sponsor Medical Monitor

d. Atypical antipsychotic medications (e.g., olanzapine and clozapine) unless on a stable dose for at least 3 months prior to screening* and dose and regimen expected to remain stable throughout the study

e. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to screening* and dose and regimen expected to remain constant during the treatment period

f. Glybera gene therapy within 2 years prior to screening*

g. Oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, and apixaban) unless on a stable dose for at least 4 weeks prior to screening* and regular clinical monitoring is performed

h. Tamoxifen, estrogens or progestins unless on a stable dose for at least 4 months prior to screening* and dose and regimen expected to remain constant during the treatment period

i. Plasma apheresis within 4 weeks prior to screening* or planned during the study

j. Prior exposure to ISIS 304801

k. Any other medication unless stable at least 4 weeks prior to screening* (Occasional or intermittent use of over-the-counter medications will be allowed at Investigator's discretion)

15. Blood donation of 50 to 499 mL within 30 days of screening* or of > 499 mL within 60 days of screening*

16. Known hypersensitivity to any of the excipients of the Study Drug (ISIS 304801 or placebo)

17. Have any other conditions, including new or worsening of existing condition, which, in the opinion of the Investigator or the Sponsor would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the study

*(Group 3) or Qualification (Groups 1 and 2)

6. STUDY PROCEDURES

6.1 Study Schedule

All required study procedures are outlined in Appendices A, B, C, and D.

6.1.1 Qualification (Groups 1 and 2)

Please refer to Section 4.1 and Appendix A.

6.1.2 Screening and Qualification (Group 3)

Before any study-specific procedures or evaluations are initiated, patients must sign and date the informed consent form. An 8-week period, including a diet stabilization period of at least 6 weeks (screening and diet stabilization period may be reduced, per Sponsor approval, if the patient is following a diet for optimal control of TGs and disease management prior to screening) is given to perform the screening evaluations. The qualification assessments will be performed at Week -2 to -1, ideally after patient eligibility has been determined, and on Study Day 1. Abnormal screening results may be retested for review by the Study Medical Monitor for eligibility purposes

6.1.3 Treatment Period

The patients, Investigators, study staff, and the Sponsor will remain blinded to lipid data through the last patient's Week 13 visit of the open-label study or until results from the database locks for the ISIS 304801-CS6 and ISIS 304801-CS16 index studies become available, whichever comes first.

During the treatment period, patients will report to the study center for clinic visits a minimum of 5 times during Weeks 1-52 (see Schedule of Procedures in Appendix A). Study Drug will be administered once weekly (Section 8.1). Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), AEs, concomitant medication/procedure information, lipid panel, volanesorsen plasma concentrations, immunogenicity (IM) testing, liver/spleen MRI, ECGs, echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Adverse events at the injection site should be collected as adverse events. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period and all patients will complete a daily food diary for one week prior to their quarterly visit. All blood and urine samples should be collected prior to volanesorsen administration. Blood sampling at Weeks 2.5, 4, 6, 8, 10, 12, 15, 17, 19, 21, 23, 25, 28, 30, 32, 34, 36, 40, 42, 44, 46, 48, and 50 may be conducted by a home healthcare nurse. Approval for study procedures to be conducted by a home healthcare nurse on other outpatient visit days will require prior approval by the Sponsor. Patients must be fasted prior to drawing all blood samples and samples drawn locally should also be sent to the central laboratory for analysis whenever possible. Every effort should be made to ensure the previous week's dose is given 7 days prior to a scheduled clinic visit. Dosing instructions and training will be provided to the patient where applicable.

All reasonable attempts should be made to ensure compliance with the visit schedule as outlined in Appendix A. However, in the event that a visit does not occur or is delayed, all subsequent visits should be calculated based on the time elapsed since Day 1 rather than from the date of the previous visit.

6.1.4 Pharmacokinetic (PK) Subgroup

A subgroup of patients will participate in an extended PK collection. Patients in this subgroup will have more frequent PK sampling over a 24-hour period following the first dose on

Study Day 1 in order to evaluate the plasma PK parameters of volanesorsen. Patients in this subgroup will have an additional visit to the clinic, or by a home healthcare nurse, on Day 2 to collect a 24-hour post-dose blood draw after dosing on Day 1. The detailed PK sampling schedules are outlined in Appendix C.

Participation in the PK subgroup is optional for sites and patients, and consent may be withdrawn for the subgroup-specific procedures (e.g., multiple blood draws for PK) without being withdrawn from the study. If a patient withdraws consent from the subgroup procedures, he/she should remain on study and continue to follow all the non-subgroup assessments and procedures as outlined in Appendix A.

6.1.5 Post-Treatment Period

After completion of the Week 52 visit assessments, patients will enter the at least 26-week post-treatment evaluation period or will participate in an expanded access program pending approval by the IRBs/IEC, and the appropriate regulatory authorities. The 26-week period consists of at least 6 Study Center visits on Weeks 54, 56, 58, 65, 71, and 78 (Weeks 54, 56, 58, and 71 may be conducted by a home healthcare nurse), as outlined in the Schedule of Procedures in Appendix A.

6.2 Additional Study Assessments

6.2.1 Laboratory Assessments

Laboratory analyte samples will be collected throughout the study. A list of these analytes is contained in Appendix B.

Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1-week and determined not to have met a stopping rule before dosing can continue.

If there is no reportable platelet count within 14 days of the last platelet count, the Investigator will contact the patient to hold dosing until a new platelet count is obtained and reviewed.

All platelet count results will be promptly reviewed by the Investigator to ensure that the count has not met the stopping rule and to determine whether the rate of decline is suggestive that the patient could be approaching the dose pause rule of 75,000/mm^3.

Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor.

6.2.2 Physical Exams and Vital Signs

Physical exams and vital signs will be performed as indicated in the Schedule of Procedures (Appendix A). Vital signs should include weight, blood pressure, pulse rate, respiratory rate and body temperature. Blood pressure and pulse rate will be recorded after the patient has been in a sitting position for at least 5 minutes. Semi-supine systolic and diastolic blood pressure should

always be measured on the same arm (preferentially on the left arm). Height will be measured at the Day 1 visit.

6.2.2.1 Eruptive Xanthoma

At each visit, patients will be asked whether they have had any episodes of eruptive xanthoma since their last visit and the number/duration of the events will be recorded. Physical exams should also include skin examination for presence/resolution of eruptive xanthomas. If a patient experiences an episode of eruptive xanthoma during the study, photos of the area should be taken, if possible.

6.2.2.2 Lipemia Retinalis

If possible, lipemia retinalis will be assessed by fundus photography prior to administration of the first dose of Study Drug (for ISIS 304801-CS16 rollover patients) and repeated at Week 52. Images will be evaluated by an independent assessor, blinded to the patient's treatment assignment.

6.2.3 Echocardiography

Echocardiography for assessment of left and right ventricular function and mitral and aortic valve function will be conducted at Week 26 and Week 52 in all patients. For the purpose of assessment of treatment-emergent changes, all echocardiograms will be evaluated on an ongoing basis by an independent central reader. Results will be provided to the DSMB for their review.

6.2.4 ECG

The ECG will be recorded after the patient has been resting in a supine position for at least 5 minutes. ECGs will be performed in triplicate at Week 13, Week 26, Week 38, Week 52, Week 65, and Week 78.

6.2.5 MRI

MRI of the liver and spleen will be conducted at Week 52 for all patients for whom MRI is not contraindicated, e.g., patients having metal implants.

MRIs will be conducted using standardized procedures and settings. MRIs will be read by an independent central reader to assess liver fat and liver and spleen size**.**

6.2.6 Quality of Life Assessments

All patients will complete Quality of Life Questionnaires (EQ-5D and SF-36) at Week 1, Week 13, Week 26, Week 52, Week 65, and Week 78.

6.2.7 Disease Symptom Diary

All patients will complete a symptom questionnaire once a week starting at the beginning of the qualification period and continuing to the end of the post-treatment follow-up period.

6.2.8 Diet Monitoring

The diets of patients enrolled in the study will be monitored as follows:

1. All patients will be required to maintain a 7-day food diary prior to Week 1, Week 13, Week 26, Week 52, Week 65, and Week 78.

2. Patients will receive diet/alcohol counseling by qualified study personnel at clinic visits throughout the course of the study. Qualified study personnel will telephone the patient to provide diet/alcohol counseling for visits that are conducted by a clinical service.

3. In addition to the 7-day food diary and the diet /alcohol counseling during clinic visits, telephone calls from a dietitian or qualified study personnel to assess as to how each patient is maintaining their diet will be conducted randomly during the treatment and post treatment follow-up periods.

6.2.9 Family History

Family history of hypertriglyceridemia and pancreatitis will be collected for each patient.

6.3 Restriction on the Lifestyle of Patients

6.3.1 Contraception Requirements

All male patients and women of childbearing potential must refrain from sperm/egg donation and either be abstinent† or, if engaged in sexual relations of child-bearing potential, practice effective contraception from the time of signing the informed consent form until at least 13 weeks after their last dose of study treatment.

Male patients must also encourage their female partner to use effective contraception from the time of signing the informed consent until 13 weeks after the subject's last dose of study treatment.

For the purposes of this Study, women of childbearing potential are defined as any female who has experienced menarche, and who does not meet 1 of the following conditions:

- Postmenopausal: 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved

- 6 weeks after surgical bilateral oophorectomy with or without hysterectomy

- Post hysterectomy

For the purposes of the study, effective contraception is defined as follows:

For male patients:

- Effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the use of condoms together with spermicidal foam/gel/film/ cream/suppository. Male patients must also encourage their female partner to use effective contraception from the time of signing the informed consent until 3 months after the patient's last dose of study treatment. Effective contraceptive for the female partner includes: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception,

intrauterine contraception/device, or barrier methods (female condom*, diaphragm, sponge, cervical cap) together with spermicidal foam/gel/film/cream/suppository. Male patients with partners that are pregnant must use condoms to ensure that the fetus is not exposed to the Study Drug.

For female patients:

- Using 1 or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or any 2 barrier methods (a combination of male or female condom* with diaphragm, sponge, or cervical cap) together with spermicidal foam/gel/film/cream/suppository.

* Note: A female condom and a male condom should not be used together as friction between the two can result in either product failing.

† Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception

6.3.2 Other Requirements

All patients will be required to fast for at least 10 hours and preferably not more than 12 hours before visits requiring fasted blood sampling.

All patients will be encouraged to follow a diet comprising ≤ 20 g fat per day during the study.

Alcohol should not be consumed during the study.

All patients will be given an instruction card that must be presented to the treating physician if a suspected case of pancreatitis occurs. The card will explain that the patient is in a clinical trial and that serum lipase and/or amylase measures should be done in order to adjudicate the event, based on Atlanta Classification (Banks et al. 2013). If serum or amylase activity is less than 3 x upper limit of normal (ULN), imaging, preferably contrast-enhanced computed tomography, should be considered to confirm the diagnosis of acute pancreatitis per the Atlanta Criteria.

7. STUDY DRUG

7.1 Volanesorsen Description

Volanesorsen drug product (ISIS 304801) characteristics are listed in Table 1.

Volanesorsen (ISIS 304801) is contained in glass prefilled syringes (PFS). Volanesorsen and its storage and preparation instructions will be provided by the Sponsor or designee. Volanesorsen must be stored securely at 2° to 8° C and be protected from light.

Table 1 Volanesorsen (ISIS 304801) Characteristics

Strength	200 mg/mL
Volume/Formulation	1.5 mL solution per PFS
Dose	300 mg once weekly
Route of Administration	SC

7.2 Packaging and Labeling

The Sponsor will provide the Investigator with packaged volanesorsen labeled (ISIS 304801) in accordance with specific country regulatory requirements.

7.3 Study Drug Accountability

The study staff is required to document the receipt, dispensing, and return/destruction of volanesorsen provided by the Sponsor. The Study Center must return all unused volanesorsen to the Sponsor or designee. All used syringes must be disposed of as per the site's hazardous waste destruction policy.

8. TREATMENT OF PATIENTS

8.1 Volanesorsen Administration

For each individual patient, volanesorsen will be administered subcutaneously as a single 1.5 mL 300 mg injection once weekly for Weeks 1-52. Patients entering this ISIS 304801-CS7 study on a reduced dose or dose frequency of Study Drug (volanesorsen), for safety or tolerability reasons in their index study (ISIS 304801-CS6 or ISIS 304801-CS16), will receive a reduced dose or dose frequency of volanesorsen for continued safety or tolerability as outlined in Sections 8.5 and 8.6. Patients entering this CS7 study having dose or dose frequency reduced in the CS16 index study after 13 weeks of treatment, as outlined in CS16 Amendment 4 Section 8.7, can receive the 300 mg once weekly dose of volanesorsen.

Patients should receive 1 dose per week, with weeks always defined relative to Study Day 1. For example if a patient receives the first dose on a Monday, subsequent doses should be given on Mondays, if possible. If a patient misses an injection, or if dosing on the usual day is not possible, the patient can reschedule the injection provided that 2 doses are administered at least 2 days apart.

Every effort should be made to ensure the previous week's dose is given 7 days prior to a scheduled clinic visit.

Please refer to the Study Drug Manual provided by the Sponsor for more detailed instructions for volanesorsen preparation and administration.

8.2 Other Protocol-Required Drugs

There are no other protocol-required drugs (Section 6.2.5).

8.3 Other Protocol-Required Treatment Procedures

There are no other protocol required treatment procedures for this study.

8.4 Treatment Precautions

There are no specific treatment precautions required for this study.

8.5 Safety Monitoring Rules

Please refer also to the 'Guidance for Investigator' section of the Investigator's Brochure.

For the purposes of safety monitoring baseline is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 (e.g., qualification assessments or assessments from the final visits of ISIS 304801-CS6 and ISIS 304801-CS16 index studies if used for qualification).

In addition to the standard monitoring of clinical safety parameters, the following guidelines are provided for the monitoring of selected parameters chosen based on preclinical and clinical observations.

Confirmation Guidance: At any time during the study (Treatment or Post-Treatment Periods), the initial clinical laboratory results meeting the safety monitoring or stopping criteria presented below **must be confirmed** by performing measurements (ideally in the same laboratory that performed the initial measurement) on new specimens. All new specimen collections should take place as soon as possible (ideally within 3 days of the initial collection). For stopping rules, if the initial laboratory result is observed during the Treatment Period, the results from the retest **must be available** prior to administering the next dose of volanesorsen.

In addition to the safety monitoring parameters listed below, the Sponsor may request confirmation of additional lab values.

Re-dosing Guidance: Patients with initial laboratory test values that reach a stopping rule must not be re-dosed until the re-test results are available. In general, patients who do not meet the stopping rules based upon retest may continue dosing. However, the Investigator and the Sponsor Medical Monitor (or appropriately qualified designee) should confer as to whether additional close monitoring of the patient is appropriate. Reduction in dose or dose frequency may also be initiated as noted in Section 8.7. If any of the stopping criteria described below (refer to Sections 8.6.1 to 8.6.3) are met, the patient will be dose paused or permanently discontinued (as described in the stopping criterion concerned) from further treatment with volanesorsen, and evaluated fully as outlined below and in consultation with the Sponsor Medical Monitor or appropriately qualified designee, and will be followed up in accordance with Section 8.8 of the protocol.

8.5.1 Safety Monitoring for Liver Chemistry Tests

The following rules are adapted from the draft guidance for industry, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," issued by the U.S. Department of Health and Human Services, Food and Drug Administration, July 2009. For a definition of Baseline please refer to guidance in Section 8.5 above.

In the event of an ALT or AST measurement that is > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) at any time during the study (Treatment or Post-Treatment Period), the initial measurement(s) should be confirmed as described above. Additional confirmatory measurements should also be performed if ALT or AST levels increase to 5 x ULN.

Frequency of Repeat Measurements: Patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) should have their liver chemistry tests (ALT, AST, alkaline phosphatase (ALP), international normalized ratio (INR) and total bilirubin) retested at least once-weekly until ALT and AST levels become ≤ 1.2 x ULN or 1.2 x baseline value if the baseline value was > ULN.

Further Investigation into Liver Chemistry Elevations: For patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), the following evaluations should be performed:

1. Obtain a more detailed history of symptoms and prior and concurrent diseases
2. Obtain further history for concomitant drug use (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
3. Obtain a history for exposure to environmental chemical agents and travel
4. Serology for viral hepatitis (HAV IgM, HBsAg, HCV antibody, CMV IgM, and EBV antibody panel)
5. Serology for autoimmune hepatitis (e.g., antinuclear antibody [ANA])

Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic CT or MRI scans, may be performed at the discretion of the Investigator, in consultation with the Sponsor Medical Monitor. Repetition of the above evaluations should be considered if a patient's ALT and/or AST levels reach 5 x ULN.

8.5.2 Safety Monitoring for Platelet Count Results

Actions to be taken in the event of reduced platelet count are shown in Table 2 in Section 8.6.3.

Additional lab tests will be determined by the Sponsor Medical Monitor or designee in consultation with the Investigator.

Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor (See also Stopping Rules Section 8.6.3).

8.5.3 Safety Monitoring for Minor Bleeding Events

Minor bleeding events are those that do not fulfill the criteria for major bleeding or clinically-relevant, non-major bleeding events (which are defined in Section 8.6.3), for example excess bruising, petechiae, gingival bleeding on brushing teeth. If a minor bleeding event occurs, the Investigator must notify the Sponsor Medical Monitor and additional testing of coagulation

parameters activated partial thromboplastin time (aPTT), prothrombin time (PT), INR and platelet count should be performed.

8.5.4 Safety Monitoring for Constitutional Symptoms

Patients will be instructed to promptly report any signs of symptoms of fever or constitutional symptoms that may arise during the study and the Investigator should closely evaluate all potential causes, including concomitant illness. Patients that experience persistent constitutional symptoms should be discussed with the Sponsor Medical Monitor or designee to determine whether additional monitoring or laboratory tests are required.

8.5.5 Safety Monitoring for LDL-C Elevations

Beginning at Week 13, laboratory alerts will be in place to notify the Investigator if a patient has a low-density lipoprotein-cholesterol (LDL-C) > 160 mg/dL (> 130 mg/dL for patients with T2DM) on 2 consecutive visits. If this occurs, LDL-C values for this patient will be unblinded for the remainder of the study and the Investigator will be encouraged to initiate/adjust treatment to lower LDL-C according to country-specific guidelines (e.g., initiate statin therapy or increase the statin dose for patients who are already on treatment).

8.5.6 Safety Monitoring for Insulin, Oral Antidiabetic Medication and Glucose

All patients on insulin will monitor their glucose levels with a glucometer as per standard practice guidelines and bring their glucometer or glucometer log printout to every clinic visit. In addition, patients who are not on insulin but use a glucometer should also bring their glucometer and/or glucometer log printout to every clinic visit.

- The Investigator or delegate will review the glucometer reading or printout at every clinic visit to evaluate if fasting pre-breakfast self-monitored plasma glucose values exceed threshold values as per the Safety Monitoring Rules for Hyperglycemia below.

All diabetic patients will note any changes in their insulin dose and /or oral antidiabetic therapy, as well as any hypoglycemic episode they may experience.

- The Investigator or delegate will ask patients at every clinic visit if they made changes in their insulin dose or oral antidiabetic therapy, and if they experienced a hypoglycemic episode.
    - Patients will be instructed on the monitoring and management of hypoglycemic episodes at each visit.
    - Documented symptomatic hypoglycemic episodes should be captured as adverse events in the adverse event CRF. Documented symptomatic hypoglycemia is defined as typical hypoglycemia symptoms accompanied by measured plasma glucose ≤ 70 mg/dL (≤ 3.9 mmol/L).
    - Any changes in insulin dose or oral antidiabetic therapy should be captured into the Concomitant Medication CRF.

8.5.7 Safety Monitoring for Documented Severe Hypoglycemia

A **documented severe hypoglycemic event** is defined as 1 in which the patient requires assistance of another person to obtain treatment for the event and has a plasma glucose level ≤ 70 mg/dL (≤ 3.9 mmol/L). The rescue treatment of hypoglycemia may include IV glucose or buccal or intramuscular glucagon.

The definition of severe symptomatic hypoglycemia includes all episodes in which neurological impairment was severe enough to prevent self-treatment and which were thus thought to place patients at risk for injury to themselves or others. Note that "requires assistance" means that the patient could not help himself or herself. Someone being kind that assists spontaneously the patient when not necessary does not qualify as "requires assistance."

Severe hypoglycemia will be qualified as a SAE only if it fulfills SAE criteria.

If a patient presents with symptoms of hypoglycemia, the Investigator will need to take immediate action to confirm the patient's glucose level and treat the patient accordingly.

The experience of hypoglycemia may vary greatly from patient to patient. However, there are certain classical signs and symptoms, of which patients should be aware as a clue that their blood glucose may be low. Common symptoms include headache, heart pounding, confusion, disorientation, numbness or tingling, pale skin, shakiness or tremulousness, increased appetite, anxiousness or nervousness, lightheadedness or dizziness, sweating, and weakness. Coma could occur if blood sugar correction is not performed.

If patients suspect they might be having a hypoglycemia reaction, they should check their blood glucose using their meters as soon as possible, before treatment if possible, provided they feel it is safe to do so. If there is doubt about safety they should treat the event first, using some sugar, milk, or juice for example, then obtain and record a blood glucose value as soon as possible thereafter. The time and nature of treatment should be noted, and especially if any blood glucose result was before or after treatment. It would be helpful for the patient to note if a contributory factor (e.g., missed or reduced meals, unaccustomed physical activity) occurred earlier in the day of the event.

8.5.8 Safety Monitoring for Hyperglycemia

Upward dose titration and/or addition of any other anti-hyperglycemic agent(s) will not be allowed during the course of the study, unless specific threshold values are met at Week 13 or later and confirmed on subsequent testing (ideally within 1-week of the initial test).

HbA1c is monitored every 3 months throughout the study. In addition, patients on insulin should self-monitor their plasma glucose (SMPG) routinely on a glucometer as per practice guidelines. If a fasting pre-breakfast SMPG value exceeds the specific glycemic limit, the patient should check it again on the following 2 days. If all the fasting pre-breakfast values on 3 consecutive days exceed the specific limit, the patient should contact the Investigator and an unscheduled central laboratory FPG measurement and HbA1c should be performed.

The threshold values are defined as:

- FPG > 270 mg/dL (15.0 mmol/L)
- HbA1c > 9% (for patients with baseline HbA1c < 8% and HbA1c increase of more than 1% from baseline (for patients with baseline HbA1c ≥ 8 and < 9%)

In case of confirmed FPG/HbA1c above the threshold value, the Investigator should ensure that no reasonable explanation exists for insufficient glucose control and in particular that:

- Plasma glucose was actually measured in the fasting condition (i.e., after at least 10 hours fast)
- Absence of intercurrent disease which may jeopardize glycemic control. In case of an emergency (e.g., surgery, infection), the Investigator can take appropriate measures for glycemic control
- Compliance to treatment is appropriate
- Compliance to diet and lifestyle is appropriate

If any of the above can reasonably explain the insufficient glycemic control, the Investigator should consider the following:

- Investigation and treatment of intercurrent disease (to be reported in adverse event (AE)/concomitant medication parts of the e-CRF)
- Stress on the absolute need to be compliant to treatment
- Organize a specific interview with a Registered Dietician or other qualified nutrition professional and stress on the absolute need to be compliant to diet and lifestyle recommendations

A FPG/HbA1c follow-up assessment should be arranged after appropriate action has been taken. If none from the above-mentioned reasons can be found, or if appropriate action fails to decrease FPG/HbA1c under the threshold values, additional medication may be introduced at the Investigator's discretion and according to local guidelines after discussion with the Sponsor Medical Monitor.

8.5.9 Acute Pancreatitis

If a patient has an episode of acute pancreatitis, dosing with Study Drug should be suspended temporarily until the patient is clinically stable. The suitability of the patient for continued dosing and the need for any modification to treatment schedule (refer to Section 8.7) will be determined by the Investigator in consultation with the Study Medical Monitor.

8.6 Stopping Rules

For the purposes of stopping rules baseline is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1.

8.6.1 Stopping Rules for Liver Chemistry Elevations

In the event of laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor,** dosing of a patient with volanesorsen will be stopped permanently; values that are not confirmed due to failure to retest or missing lab values will be presumed confirmed:

1. ALT or AST > 8 x ULN, which is confirmed
2. ALT or AST > 5 x ULN, which is confirmed and persists for ≥ 2 weeks
3. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed **and** total bilirubin > 2 x ULN or INR > 1.5
4. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed, and the new appearance (i.e., onset coincides with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> ULN) felt by the Investigator to be potentially related to hepatic inflammation

8.6.2 Stopping Rules for Renal Function Test Results

In the event of a persistent elevation that is observed over 2 consecutive weeks, for any of the 3 criteria below, dosing of a patient with volanesorsen may be stopped temporarily:

1. Serum creatinine increase that fulfill all of the following criteria: ≥ 0.3 mg/dL (26.5 µmol/L) and ≥ 40% above baseline creatinine values and > ULN
2. Proteinuria, dipstick 2 + (confirmed by dipstick retest and then further confirmed by a quantitative total urine protein measurement of > 1.0 g/24-hour)
3. Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault ≤ 40 mL/min that is confirmed by a 24-hour urine collection

The possible dosing re-initiation or follow-up schedule for any events meeting either of these criteria will be determined by the Investigator **in consultation with** the Sponsor Medical Monitor or designee.

8.6.3 Stopping Rules for Platelet Count Results

Actions to be taken in the event of a low platelet count are summarized in Table 2 below.

In the event of a platelet count less than 75,000/mm^3 that is associated with major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with volanesorsen will be stopped permanently. The follow-up schedule for any events meeting this stopping criterion will be determined by the Investigator in consultation with the Sponsor Medical Monitor.

In the event of any platelet count less than 50,000/mm^3, or a rate of decline ≥ 50% between two consecutive assessments, irrespective of the platelet level, then dosing of a patient with volanesorsen will be stopped permanently. Platelet count will be monitored daily until 2 successive values show improvement then monitored every 2-3 days until platelet count is stable.

Administration of steroids is recommended for patients whose platelet count is less than 25,000/mm^3. Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (**note:** may require continuation with oral steroids after methylprednisolone). In order to reduce the unlikely but potential increased risk of pancreatitis during the period of corticosteroid therapy, triglyceride levels will be monitored weekly during corticosteroid treatment and the laboratory alert will be changed from an increase of 2,000 to 500 mg/dL during that period.

In the event of a platelet count less than 75,000/mm^3, and in the absence of major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with volanesorsen should be suspended temporarily until the platelet count has recovered to> 100,000/mm^3. If dosing is continued it should be at a reduced dose frequency of 300 mg every 2 weeks or a reduced dose of 150 mg per week (refer to Section 8.7). The suitability of the patient for continued dosing will be determined by the Investigator in consultation with the Study Medical Monitor and will be based on factors such as the original rate of decline in the patient's platelet count, whether any bleeding events were experienced by the patient, and the speed of recovery of platelet count upon holding of dosing.

If after the first dosing rechallenge the platelet count again falls below 75,000/mm^3, then dosing of the patient with Study Drug will be stopped permanently.

Following a rechallenge platelet count should be tested every week until count is stable.

Any unreportable platelet count result must be rechecked and determined not to have met a stopping rule before dosing can continue.

If there is no reportable platelet count within 14 days of the last platelet count, the Investigator will contact the patient to hold dosing until a new platelet count is obtained and reviewed.

Definition of Major Bleeding Events (Schulman et al. 2005):

- Fatal bleeding, and/or
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarterial or pericardial, or intramuscular with compartment syndrome, and/or
- Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more within 24 hours, or leading to transfusion of 2 or more units of whole or red cells

Definition of Clinically-Relevant, Non-Major Bleeding Events (Schulman et al. 2005):

1. Multiple-source bleeding
2. Spontaneous hematoma > 25 cm^2
3. Excessive wound hematoma (not injection site related)

4. Macroscopic hematuria (spontaneous or lasting > 24 hours if associated with an intervention)
5. Spontaneous rectal bleeding; epitasis, gingival bleeding, hemoptysis, hematemesis
6. Bleeding after venipuncture for > 5 minutes

Table 2 Actions in Patients with Low Platelet Count

Platelet Count on Rx	Drug Dose	Monitoring
Normal range, > 140K/mm^3	No action	Monitor every 2 weeks
100K-140K/mm^3	No action	Closer observation Monitor every 1-week until stable*
75K-100K/mm^3	Permanently reduce dose frequency to 300 mg every 2 weeks or reduce dose to 150 mg weekly	Closer observation Monitor every 1-week
50K-75K/mm^3	If occurs while on dose of 300 mg every 2 weeks or 150 mg every week then permanently discontinue Study Drug, otherwise dose pause. When platelet count returns to > 100K/mm^3 restart dosing at dose frequency of 300 mg every 2 weeks or 150 mg weekly **only if approved by Sponsor Medical Monitor**	Closer observation Monitor every 2-3 days until 2 successive values show improvement Consider discontinuation of antiplatelet agents/NSAIDS/ anticoagulant medication
25K-50K/mm^3 or a rate of decline ≥ 50% between two consecutive assessments, irrespective of the platelet level	Permanently discontinue Study Drug	Closer observation Monitor daily until 2 successive values show improvement then monitor every 2-3 days until platelet count stable Discontinue antiplatelet agents/NSAIDS/anticoagulant medication while platelet count < 50K/mm^3 if possible
< 25K/mm^3	Permanently discontinue Study Drug	Closer observation: Monitor daily until 2 successive values show improvement then monitor every 2-3 days until platelet count stable Steroids recommended** Consider need for hospitalization and referral to hematologist Discontinue antiplatelet agents/NSAIDS/anticoagulant medication while platelet count < 50K/mm^3 if possible

* At least 3 consecutive values measured weekly that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3

** Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (**note**: may require continuation with oral steroids after methyl prednisolone). In order to reduce the unlikely but potential increased risk of pancreatitis during the period of corticosteroid therapy, triglyceride levels will be monitored weekly during corticosteroid treatment and the laboratory alert will be changed from an increase of 2,000 to 500 mg/dL during that period.

8.7 Adjustment of Dose Frequency

Dose adjustments for platelet count reduction must be made in accordance with Section 8.6.3 and Table 2 (above).

Other dose adjustments, including dose interruptions, and/or decreasing the dose or dose frequency will be allowed for safety and tolerability. Any proposed adjustment to treatment schedule must be discussed with, and approved by, the Study Medical Monitor prior to initiation. Up to 2 adjustments in the treatment schedule may be allowed.

Patients may be dose paused in response to AEs after consultation with Study Medical Monitor.

8.8 Discontinuation of Study Treatment

A patient must permanently discontinue study treatment for any of the following:

- The patient becomes pregnant. Report the pregnancy according to instructions in Section 9.5.4
- The patient withdraws consent
- The patient experiences an AE that necessitates permanent discontinuation of study treatment
- The patient develops laboratory test abnormalities that meet any of the stopping rules listed in Section 8.6

The reason for discontinuation of study treatment must be recorded in the CRF and source documentation.

8.8.1 Follow-up Visits for Early Termination from Treatment Period

Any patient who discontinues early from the Treatment Period should be followed as per the platelet monitoring rules shown in Table 2 in Section 8.6.3 for the first 6 weeks after discontinuing Study Drug. Following this period, if the platelet count is stable (at least 3 consecutive values that are stable as determined by the Sponsor Medical Monitor and $> 100{,}000/mm^3$), the next platelet count should be taken within at least 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug. Patients should also be strongly encouraged to attend applicable landmark visits at Weeks 12, 13, 25, 26, and 50, 52 (calculated based on the time elapsed since Day 1) to collect fasting lipid panels and conduct safety assessments in accordance with the Schedule of Procedures in Appendix A. Any patient who discontinues treatment after Week 44 should also be strongly encouraged to attend a final follow-up visit (Week 78 visit assessments) approximately 26 weeks after their last dose of Study Drug, in addition to the applicable landmark visits.

If the patient declines or is unable to participate in the above, an early termination (ET) visit (Week 52 visit assessments) should be performed at the time of withdrawal, at a minimum, and ideally within 2 weeks from the last dose of Study Drug.

8.8.2 Follow-up Visits for Early Termination from Post-Treatment Follow-up Period

The patient who requests to withdraw from the study during the Post-Treatment Follow-up Period should be encouraged to follow the platelet monitoring rules shown in Table 2 in Section 8.6.3 for the first 6 weeks after discontinuing Study Drug. Following this period, if the platelet count is stable (at least 3 consecutive values that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3), the next platelet count should be taken within at least 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug. Patients should also be encouraged to undergo a final follow-up visit (Week 78, see Appendix A) prior to leaving the study.

If a patient withdraws due to an AE at any time during the study, the Investigator should arrange for the patient to have appropriate follow-up until the AE has resolved or stabilized.

8.9 Withdrawal of Patients from the Study

Patients must be withdrawn from the study for any of the following:

- Withdrawal of consent
- The patient is unwilling or unable to comply with the protocol

Other reasons for withdrawal of patients from the study might include:

- At the discretion of the Investigator for medical reasons
- At the discretion of the Investigator or Sponsor for noncompliance
- Significant protocol deviation

All efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information, including the reason for withdrawal from study, must be recorded in the CRF.

Any patient who withdraws consent to participate in the study will be removed from further treatment and study observation immediately upon the date of request. These patients should be encouraged to complete the ET study procedures and observations at the time of withdrawal (see Section 8.8 and Appendix A).

For patients withdrawn for reasons other than withdrawal of consent every effort should be made to complete the early termination study procedures and observations at the time of withdrawal (see Section 8.8 and Appendix A).

8.10 Concomitant Therapy and Procedures

The use of concomitant therapies or procedures defined below must be recorded on the patient's CRF. AEs related to administration of these therapies or procedures must also be documented on the appropriate CRF.

8.10.1 Concomitant Therapy

A concomitant therapy is any non-protocol specified drug or substance (including over-the-counter medications, herbal medications and vitamin supplements) administered between signing informed consent and completion of the post-treatment follow-up period. All concomitant medications/treatments and significant non-drug therapies (including supplements and assistive devices) received by a patient, including changes in the patient's current medications, must be recorded in the patient's source documents and CRF. Patients taking over the counter (OTC) omega-3 fatty acids should make every effort to remain on the same brand throughout the study.

Allowed Concomitant Therapy

Any medications deemed necessary by the Investigator are allowed except those listed in the disallowed concomitant therapy.

Disallowed Concomitant Therapy

No lipid lowering therapies (e.g., fibrates, niacin, fish oil or other products containing omega-3 fatty acids [including OTC preparations]), -glucagon-like peptide-1 (GLP-1) agonists, Glybera, or systemic corticosteroids may be started or adjusted after baseline qualification. Doses of existing oral anti-diabetic medication, oral contraceptives, hormone replacement therapy, anticoagulants, or drugs or dietary supplements with potential lipid-altering effects should not be adjusted. Study patients are prohibited from receiving other experimental agents during the study. This includes marketed agents at experimental dosages that are being tested for the treatment of hypertriglyceridemia.

Patients should consult with the Site Investigator or designee prior to initiating any new medication, including non-prescription or herbal compounds or any other non-drug therapy.

8.10.2 Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between signing of informed consent and Week 78 visit.

Disallowed Concomitant Procedure

Plasma apheresis is not allowed during the study.

8.11 Treatment Compliance

Compliance with treatment dosing is to be monitored and recorded by Study Center staff. The Study Center staff is required to document the receipt, dispensing, and return/destruction of volanesorsen. Patients that are self-administering volanesorsen at home must record treatment in a dosing diary that will be reviewed periodically by Study Center staff and the Clinical Monitor.

9. SERIOUS AND NON-SERIOUS ADVERSE EVENT REPORTING

9.1 Sponsor Review of Safety Information

Safety information will be collected, reviewed, and evaluated by the Sponsor in accordance with the Safety Management Plan throughout the conduct of the clinical trial.

9.2 Regulatory Requirements

The Sponsor is responsible for regulatory submissions and reporting to the Investigators of serious adverse events (SAEs) including suspected unexpected serious adverse reactions (SUSARs) per the International Conference on Harmonization (ICH) guidelines E2A and ICH E6. Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines.

Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) will be notified of any SAE according to applicable regulations. The Independent DSMB will be notified of any SAE as specified in the DSMB charter.

In addition to the Investigator's assessment of relatedness, the Sponsor or designee will evaluate the available information and perform an independent assessment of relatedness. While the Sponsor may upgrade an Investigator's decision it is not permissible to downgrade the Investigator's opinion for the purposes of determining whether the SAE meets the definition of a SUSAR.

The following table identifies the SAEs that the Sponsor or designee will not report on an individual basis in an expedited manner because they are anticipated to occur in the study population independent of volanesorsen exposure. The Investigator still has the responsibility to report all SAEs to the Sponsor as described in Sections 9.4.1 to 9.4.3.5.

Table 3 Expected Event for the Protocol Defined Population by Preferred Term and the Expected Incidence

Preferred Term	Expected Incidence in the Protocol Defined Population (Gaudet et al. 2010 and 2013)
Pancreatitis associated events including the PTs of hereditary pancreatitis, pancreatitis, pancreatitis acute, pancreatitis chronic, pancreatitis necrotizing, pancreatitis relapsing	0.2-0.35 events per patient-year

Fatal pancreatitis associated events will be considered as unexpected and are reportable. The Sponsor and DSMB will monitor non-fatal pancreatitis associated SAEs using the incidence rate of the event compared to the rate expected in a non-volanesorsen exposed population. If the aggregate analysis indicates that an event is occurring significantly more frequently or at a greater severity than expected, then the event will be reported.

SAEs not specified in the table will be evaluated on case by case basis to determine whether there is a reasonable possibility that the drug caused the event. If the event is considered by the Sponsor or designee to meet the definition of a SUSAR the event will be reported.

9.3 Definitions

9.3.1 Adverse Event

An adverse event is any unfavorable and unintended sign (including a clinically-significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the

study or use of investigational drug product, whether or not the AE is considered related to the investigational drug product.

9.3.2 Adverse Reaction and Suspected Adverse Reaction

An adverse reaction is any adverse event caused by volanesorsen.

A suspected adverse reaction is any adverse event for which there is a reasonable possibility that volanesorsen drug caused the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

9.3.3 Serious Adverse Event (SAE)

A serious adverse event is any adverse event that in the view of either the Investigator or Sponsor, meets any of the following criteria:

- Results in death
- Is life threatening: that is, poses an immediate risk of death at the time of the event

An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Hospitalization is defined as an admission of greater than 24 hours to a medical facility and does not always qualify as an AE
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly or birth defect in the offspring of the patient (whether the patient is male or female)
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

9.4 Monitoring and Recording Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the study (i.e., before informed consent) should be recorded as Medical History and not recorded as AEs unless the pre-existing condition worsened. The Investigator should always group signs and symptoms into a single term that constitutes a **single unifying diagnosis** if possible.

9.4.1 Serious Adverse Events

In the interest of patient safety, and in order to fulfill regulatory requirements**,** all SAEs (regardless of their relationship to volanesorsen) should be reported to the Sponsor or designee within 24 hours of the Study Center's first knowledge of the event. The collection of SAEs will begin after the patient signs the informed consent form and stop at the end of the patient's follow-up period which is defined as the Week 78 visit. When the Investigator is reporting by telephone, it is important to speak to someone in person versus leaving a message. An Initial Serious Adverse Event Form should be completed and a copy should be faxed to the Sponsor or designee.

Detailed information should be actively sought and included on Follow-Up Serious Adverse Event Forms as soon as additional information becomes available. All SAEs will be followed until resolution. SAEs that remain ongoing past the patient's last protocol-specified follow-up visit will be evaluated by the Investigator and Sponsor. If the Investigator and Sponsor agree the patient's condition is unlikely to resolve, the Investigator and Sponsor will determine the follow-up requirement.

9.4.2 Non-Serious Adverse Events

The recording of non-serious AEs will begin after the patient signs the informed consent form and will stop at the end of the patient's follow-up period, which is defined as the Week 78 visit. The Investigator will monitor each patient closely and record all observed or volunteered AEs on the Adverse Event Case Report Form.

9.4.3 Evaluation of Adverse Events (Serious and Non-Serious)

The Investigator's opinion of the following should be documented on the Adverse Event Case Report Form:

9.4.3.1 Relationship to the Study Drug

The event's relationship to volanesorsen is characterized by 1 of the following:

- **Related:** There is clear evidence that the event is related to the use of volanesorsen, e.g., confirmation by positive rechallenge test
- **Possible:** The event cannot be explained by the patient's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and volanesorsen administration
- **Unlikely/Remote:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to volanesorsen administration and/or exposure suggests that a causal relationship is unlikely (For reporting purposes, Unlikely/Remote will be grouped together with Not Related)
- **Not Related:** The event can be readily explained by the patient's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and volanesorsen

9.4.3.2 Severity

The severity of AEs and SAEs will be graded based on criteria from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010 (refer to Appendix D). Any AE not listed in Appendix D will be graded as follows:

- **Mild:** The event is easily tolerated by the patient and does not affect the patient's usual daily activities
- **Moderate:** The event causes the patient more discomfort and interrupts the patient's usual daily activities
- **Severe:** The event is incapacitating and causes considerable interference with the patient's usual daily activities

If the event is an SAE, then all applicable seriousness criteria must be indicated (criteria listed in Section 9.3.3).

9.4.3.3 Action Taken with Volanesorsen

Action taken with volanesorsen due to the event is characterized by 1 of the following:

- **None:** No changes were made to volanesorsen administration and dose
- **Permanently Discontinued:** Volanesorsen was discontinued and not restarted
- **Temporarily Interrupted, restarted – same dose:** Dosing was temporarily interrupted or delayed due to the AE and restarted at the same dose
- **Reduced schedule:** Dosing frequency was reduced

9.4.3.4 Treatment Given for Adverse Event

Any treatment (e.g., medications or procedures) given for the AE should be recorded on the Adverse Event Case Report Form (treatment should also be recorded on the concomitant treatment or ancillary procedures CRF as appropriate).

9.4.3.5 Outcome of the Adverse Event

If the event is a non-serious AE then the event's outcome is characterized by 1 of the following:

- **AE Persists:** Patient terminates from the trial and the AE continues
- **Recovered:** Patient recovered completely from the AE
- **Became Serious:** The event became serious (the date that the event became serious should be recorded as the Resolution Date of that AE and the Onset Date of the corresponding SAE)
- **Change in Severity** (if applicable): AE severity changed

If the event is a SAE then the event's outcome is characterized by 1 of the following:

- **Ongoing:** SAE continuing
- **Persists (as non-serious AE):** Patient has not fully recovered but the event no longer meets serious criteria and should be captured as an AE on the non-serious AE eCRF (the SAE resolution date should be entered as the date of onset of that AE)
- **Recovered:** Patient recovered completely from the SAE (the date of recovery should be entered as the SAE resolution date)
- **Fatal:** Patient died (the date of death should be entered as the SAE resolution date)

9.4.4 Adjudication Committees

All SAEs that occur during the study that are consistent with a major acute cardiovascular event (MACE) will be adjudicated by a blinded, independent committee as outlined in the MACE Adjudication Charter.

All AEs and SAEs that occur during the study that are consistent with an event of acute pancreatitis will be adjudicated by a blinded, independent committee according to the Atlanta classification of acute pancreatitis (Banks et al. 2013) and as outlined in the Pancreatitis Adjudication Charter. In addition, data for prior episodes of acute pancreatitis or suspected pancreatitis will be collected by review of each patient's medical chart and these events will also be adjudicated.

9.5 Procedures for Handling Special Situations

9.5.1 Abnormalities of Laboratory Tests

Clinically-significant abnormal laboratory test results may, in the opinion of the Investigator, constitute or be associated with an AE. Examples of these include abnormal laboratory results that are associated with symptoms, or require treatment, e.g., bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac arrhythmias due to hyperkalemia. Whenever possible, the underlying diagnosis should be listed in preference to abnormal laboratory values as AEs. Clinically-significant abnormalities will be monitored by the Investigator until the parameter returns to its baseline value or until agreement is reached between the Investigator and Sponsor Medical Monitor. Laboratory abnormalities deemed not clinically-significant (NCS) by the Investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator should not be deemed NCS on the laboratory sheet.

The Investigator is responsible for reviewing and signing all laboratory reports. The signed clinical laboratory reports will serve as source documents and should include the Investigator's assessment of clinical significance of out of range/abnormal laboratory values.

9.5.2 Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the patient is hospitalized; the Study Center must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the patient's consent to participate in the study
- The condition that required the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the patient's consent to participate in the study and the timing of the procedure or treatment
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission

9.5.3 Dosing Errors

Volanesorsen dosing errors should be documented as Protocol Deviations. A brief description should be provided in the deviation, including whether the patient was symptomatic (list symptoms) or asymptomatic, and the event accidental or intentional.

Dosing details should be captured on the Dosing Case Report Form. If the patient takes a dose of volanesorsen that exceeds protocol specifications and the patient is symptomatic, then the symptom(s) should be documented as an AE and be reported per Section 9.4.

Should an overdose occur, the Investigator or designee should refer to the Guidance to Investigator's section of the Investigator's Brochure and contact the Sponsor or designee within 24 hours.

9.5.4 Contraception and Pregnancy

Male patients and female patients of childbearing potential must continue to use appropriate contraception with their partners, or refrain from sexual activity, as described in Section 6.3.1.

If a patient becomes pregnant or a pregnancy is suspected, or if a male patient makes or believes that he has made someone pregnant during the study, then the Study Center staff must be informed immediately. An Initial Pregnancy Form should be submitted to the Sponsor or designee **within 24 hours** of first learning of the occurrence of pregnancy. Follow-up information including delivery or termination is reported on Follow-up Pregnancy Forms and reported within 24 hours.

Payment for all aspects of obstetrical care, child or related care will be the patient's responsibility.

Female patients: If a suspected pregnancy occurs while on the study (including follow-up), a pregnancy test will be performed. The patient with a confirmed pregnancy will be immediately withdrawn from treatment with volanesorsen. However, the patient will be encouraged to complete the post-treatment follow-up portion of the study to the extent that study procedures do not interfere with the pregnancy. Regardless of continued study participation, the study physician will assist the patient in getting obstetrical care and the progress of the pregnancy will be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the Study Center and Sponsor may require access to the mother and infant's medical records for an additional 8 weeks after birth.

Male patients: The progress of the pregnancy in a male patient's partner should be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, **the Study Center and Sponsor may request access to the mother and infant's medical records for an additional 8 weeks after birth**. Follow-up will be performed to the extent permitted by applicable regulations and privacy considerations.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints

For fasting lipid measurements, the values at Month 3 analysis time point are defined as the average of Week 12 (Day 78) and Week 13 (Day 85) fasting assessments, the values of Month 6 analysis time point is at the end of Month 6 are defined as the average of Week 25 (Day 169) and Week 26 (Day 176) fasting assessments, and the values at the Month 12 analysis time point are defined as the average of Week 50 (Day 344) and Week 52 (Day 358) fasting assessments.

10.1.1 Efficacy Endpoints

- Percent change and absolute change from baseline in fasting TG
- Frequency and severity of patient reported abdominal pain during the treatment period
- Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-HDL-C, apoB, HDL-C, apolipoprotein A-1 (apoA-1), VLDL-C, and LDL-C
- Percent change from baseline in fasting total apolipoprotein C-III
- Quality of Life questionnaires (EQ-5D, SF-36)
- Adjudicated acute pancreatitis event rate
- Other symptoms: eruptive xanthoma, lipemia retinalis

10.1.2 Safety Endpoints

- Adverse events including adjudicated events of pancreatitis and MACE
- Vital signs and weight
- Physical examinations
- Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis)
- Echocardiography
- Electrocardiograms (ECGs)
- Use of concomitant medications
- MRIs

10.2 Sample Size

No sample size calculations were performed as this is an open-label study.

10.3 Populations

Full Analysis Set (FAS): All patients who are enrolled and have a baseline TG assessment. The FAS represents the practically-feasible intent-to-treat (ITT) population as delineated in ICH Guideline E9.

Per Protocol Set (PPS): Subset of the FAS who received 9 of first 13 scheduled doses of volanesorsen and with no significant protocol deviations that would be expected to affect efficacy and PD assessments. The detailed criteria will be specified and finalized prior to the final database lock.

Safety Set: All patients who are enrolled and receive at least 1 dose of volanesorsen.

PK Population: All patients who are enrolled, receive at least 1 dose of volanesorsen, and have at least 1 evaluable PK sample collected, analyzed, and reported.

10.4 Definition of Baseline

Definitions of baseline are given below for the purposes of the final analysis.

For fasting lipid measurements, 2 baselines are defined for each patient in Groups 1 and 2: Group 1 (ISIS 304801-CS6) or Group 2 (ISIS 304801-CS16) index study baseline and the baseline in this open-label study, which is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 (e.g., qualification assessments or assessments from final visit of the ISIS 304801-CS6 or ISIS 304801-CS16 index studies if used for qualification).

For other measurements, baseline for patients on active treatment in the ISIS 304801-CS6 or ISIS 304801-CS16 index study will be the ISIS 304801-CS6 or ISIS 304801-CS16 index study baseline. For patients on placebo in the ISIS 304801-CS6 or ISIS 304801-CS16 index study, baseline for safety will be the last non-missing assessment prior to the first dose of Study Drug.

10.5 Interim Analysis

An interim analysis may be conducted after the last patient's Week 13 visit of the open-label study or after the database of the ISIS 304801-CS6 and ISIS 304801-CS16 index studies are locked and unblinded. Both safety and efficacy information from this open-label study may be summarized during this interim analysis. Efficacy analyses will be detailed in the SAP.

10.6 Planned Methods of Analysis

All eCRF data, lab data transfers, as well as any outcomes derived from the data, will be provided in the patient data listings. Patient data listings will be presented for all patients enrolled into the study. Descriptive summary statistics including n, mean, median, standard deviation, standard error, interquartile range (25th percentile, 75th percentile), and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data by treatment group. Where appropriate, p-values will be reported. All statistical tests will be conducted using 2-sided tests with 5% Type I error rates unless otherwise stated.

All efficacy endpoints will be assessed in the FAS and PPS. All safety assessments will be performed on the Safety Set. PK endpoints will be assessed in the PK Set as applicable.

10.6.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics by treatment group. The patient disposition will be summarized by treatment group of the index studies. All patients enrolled will be included in a summary of patient disposition.

10.6.2 Safety Analysis

Treatment duration and amount of Study Drug received will be summarized by treatment group of the index studies.

Patient incidence rates of AEs will be tabulated by MedDRA system organ class, MedDRA preferred term, and treatment group of the index studies. Narratives of treatment-emergent deaths, serious and significant AEs, including early withdrawals due to AEs, will also be provided.

All treatment-emergent AEs, all treatment-emergent AEs potentially related to Study Drug, all treatment-emergent serious AEs, and all treatment-emergent serious AEs potentially related to Study Drug will be summarized.

Injection Site Reactions (ISRs) will be summarized by treatment group of the index studies, MedDRA preferred term and severity.

Independently adjudicated events of MACE and pancreatitis will be summarized by treatment group of the index studies.

Laboratory tests to ensure patient safety including chemistry panel, complete blood count (CBC) with differential, coagulation panel, IM, complement etc., will be summarized by study visits by treatment group of the index studies.

These safety variables will also be presented as change and percent change from baseline over time after Study Drug administration, as appropriate.

Vital signs, weight, ECG measures, echocardiography assessments, and MRI assessments will be tabulated by treatment group of the index studies.

10.6.3 Efficacy Analysis

Percent change and change from baseline to Month 3, Month 6, and Month 12 in fasting TG will be summarized by treatment group of the index studies. Response rate of patients with fasting plasma TG < 750 mg/dL or achieving fasting TG $\geq 40\%$ reduction from baseline at Month 3, Month 6, and Month 12 will be summarized. Response analysis will also be conducted using a range of fasting plasma TG thresholds for determination of responder status.

Percent change and change from baseline to Month 3, Month 6, and Month 12 will also be summarized by treatment group of the index studies for other fasting lipid measures including non-HDL-C, apoB, HDL-C, apoA-1, VLDL-C, and LDL-C, total cholesterol, and fasting total apoC-III.

The incremental effects of volanesorsen on lipid measures will be explored and the association between changes in lipid parameters and total amount of drug received will be examined, as appropriate.

Frequency and severity of patient reported abdominal pain, adjudicated acute pancreatitis event rate, quality of life assessments, and comparison of other symptoms including eruptive xanthomas and lipemia retinalis will be summarized by treatment group of the index studies.

Additional details of the analyses to be conducted will be provided in the SAP.

10.6.4 Pharmacokinetic and Immunogenicity Analysis

10.6.4.1 Pharmacokinetic Analysis

For all patients, pre-dose and post-treatment volanesorsen plasma concentrations will be summarized using descriptive statistics, with stratification for Group 1 and 2 patients by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16 and IM status.

For patients in the PK subgroup only, non-compartmental PK analysis of volanesorsen will be carried out on each individual patient data set using data collected in the open-label study from the intensive PK subgroup, following a single-dose (i.e., single-dose PK) or multiple doses (i.e., steady-state PK), depending on their earlier treatment in the index studies (Group 1 and 2 patients). On Week 1 Day 1 of the open-label study, patients who received placebo in the index study (and all patients in Group 3) will receive the first treatment of volanesorsen (single-dose PK), while patients who received volanesorsen in the index studies had been on volanesorsen treatment for 12 months (ISIS 304801-CS6) or 6 months (ISIS 304801-CS16), thus the PK data collected from these patients reflect steady-state PK. The maximum observed drug concentration (C_{max}) and the time taken to reach C_{max} (T_{max}) will be obtained directly from the concentration-time data. Area under the plasma concentration-time curve from time zero to 24 hours ($AUC_{0\text{-}24hr}$) will be calculated using the linear trapezoidal rule. Apparent systemic (plasma) clearance after SC administration ($CL_{0\text{-}24hr}/F_{0\text{-}24hr}$) will be calculated from $CL_{0\text{-}24hr}/F_{0\text{-}24hr}$ = Actual Dose/$AUC_{0\text{-}24hr}$. Mean residence time (MRT) from time zero to 24 hours after the SC administration will be calculated from the equation, $MRT_{0\text{-}24hr} = AUMC_{0\text{-}24hr}/AUC_{0\text{-}24hr}$, where $AUMC_{0\text{-}24hr}$ is the area under the moment plasma concentration-time curve from time zero to 24 hours after the SC administration. Other PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist.

Plasma PK parameters will be summarized using descriptive statistics, with and without stratification by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16 and IM status. Additional details regarding the PK analysis will be described in the SAP.

Population PK, PK/PD, and covariate analysis may be performed if deemed appropriate, and results will be reported separately.

10.6.4.2 Immunogenicity Analysis

Immunogenicity (IM) results (screen positive/negative, confirmed positive/negative or not evaluable, and when applicable, titer of anti-volanesorsen antibodies) before, during, and after treatment with Study Drug (volanesorsen) (i.e., sample [anti-drug antibody] ADA status) will be

listed by their prior treatment in study ISIS 304801-CS6 or ISIS 304801-CS16 (Groups 1 and 2) and study day. Subject ADA status (positive/negative or not evaluable) for all evaluable patients, along with the study day associated with the first positive IM status emerged (T_{first}, i.e., onset of ADA development), the last positive IM status observed (T_{last}), the duration of ADA response (number of days between T_{first} and T_{last}) if appropriate, the last ADA sample collection day, and subject - peak titer if applicable, will be listed by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16 (Groups 1 and 2) and study day. Subjects with positive anti-volanesorsen antibody status may be further classified (when applicable) as being either 'persistent', 'transient', or 'not determinable', if deemed appropriate.

Additionally, the sample and subject IM incidence (number) and incidence rate (percent) will be summarized as the total number and percent of evaluated subjects with antibody negative, positive, and unknown status by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16. Furthermore, onset, duration, and titer of the ADA response, if applicable, will be summarized as median, quartiles (25% and 75%), and range.

Additional details regarding the IM data analysis will be described in the SAP.

Potential relationships between immunogenicity results (e.g., IM status) and selected efficacy (e.g., %change in fasting TG from baseline at 3-, 6-, and 12-month endpoints), safety, and PK (e.g., C_{trough}) measures will be evaluated using graphical analysis and statistical analysis. These analyses will be either conducted and included in the study report, or data pooled and analyzed from all available Phase 2 and 3 studies and reported separately.

11. INVESTIGATOR'S REGULATORY OBLIGATIONS

11.1 Informed Consent

The written informed consent document should be prepared in the language(s) of the potential patient population, based on an English version provided by the Sponsor.

Before a patient's participation in the trial, the Investigator is responsible for obtaining written informed consent from the patient after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific qualification procedures or any Study Drug are administered. The patient must be given sufficient time to consider whether to participate in the study.

The acquisition of informed consent and the patient's agreement or refusal to notify his/her primary care physician should be documented in the patient's medical records and the informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion (not necessarily an Investigator). The original signed informed consent form should be retained in the Study Master File and in any other locations required by institutional policy, and a copy of the signed consent form should be provided to the patient.

11.2 Ethical Conduct of the Study

The Guidelines of the World Medical Association (WMA) Declaration of Helsinki dated October 2002 the applicable regulations and guidelines of current Good Clinical Practice (GCP) as well as the demands of national drug and data protection laws and other applicable regulatory requirements will be strictly followed.

11.3 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent form, other written patient information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by the Sponsor before recruitment of patients into the study and shipment of volanesorsen. A copy of the written approval of any other items/materials that must be approved by the Study Center or IEC/IRB must also be received by the Sponsor before recruitment of patients into the study and shipment of Study Drug. The Investigator's Brochure must be submitted to the IEC/IRB for acknowledgement.

The Investigator must submit to and, where necessary, obtain approval from the IEC/IRB, for all subsequent protocol amendments and changes to the informed consent document. The Investigator should notify the IEC/IRB of deviations from the protocol in accordance with ICH GCP Section 4.5.2. The Investigator should also notify the IEC/IRB of serious adverse events occurring at the Study Center and other adverse event reports received from the Sponsor, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study. Copies of the Investigator's reports, all IEC/IRB submissions and the IEC/IRB continuance of approval must be sent to the Sponsor.

11.4 Patient Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained. On the case report forms (CRF) or other documents submitted to the Sponsor, patients should be identified by unique initials and a patient study number only. Documents that are not for submission to the Sponsor (e.g., signed informed consent forms) should be kept in strict confidence by the Investigator.

In compliance with Federal and local regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the patient to permit named representatives to have access to his/her study-related records without violating the confidentiality of the patient.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments

Protocol amendments must be made only with the prior approval of the Sponsor. Agreement from the Investigator must be obtained for all protocol amendments and amendments to the informed consent document. The regulatory authority and IEC/IRB must be informed of all amendments and give approval for any amendments likely to affect the safety of the patients or the conduct of the trial. The Investigator **must** send a copy of the approval letter from the IEC/IRB to the Sponsor.

12.2 Study Termination

The Sponsor reserves the right to terminate the study according to the terms of the site contract. The Investigator reserves the right to terminate their participation in the study, according to the terms of the site contract. The Investigator/Sponsor should notify the IEC/IRB in writing of the trial's completion or early termination and send a copy of the notification to the Sponsor.

12.3 Study Documentation and Storage

An electronic case report form (eCRF) utilizing an Electronic Data Capture (EDC) application will be used for this study.

The Investigator should ensure that all appropriately qualified persons to whom he/she has delegated trial duties are recorded on a Sponsor-approved Delegation of Site Responsibilities Form.

Source documents are original documents, data, and records from which the patient's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, imaging, and correspondence. In this study, CRFs may not be used as source documents.

The Investigator and Study Center staffs are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation in accordance with Section 8 of the ICH Guidelines (E6), suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Elements should include:

- Patient files containing completed CRFs, informed consents, and supporting copies of source documentation
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation and all correspondence to and from the IEC/IRB and the Sponsor
- If volanesorsen supplies are maintained at the Study Center, proof of receipt, volanesorsen Accountability Record, Return of volanesorsen for Destruction, final study volanesorsen reconciliation, and all volanesorsen-related correspondence

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

No study document should be destroyed without prior written agreement between the Sponsor or and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor.

12.4 Study Monitoring

The Sponsor representative and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the trial (e.g., CRFs and other pertinent data) provided that patient confidentiality is respected.

The Sponsor monitor is responsible for inspecting the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to patient medical records and other study-related records needed to verify the entries on the CRFs.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's Clinical Quality Assurance Department. Inspection of Study Center facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the trial conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

To ensure the quality of clinical data a clinical data management review will be performed on patient data received by the Sponsor. During this review, patient data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or Study Center notifications will be sent to the Study Center for completion and return to Sponsor.

The Principal Investigator will sign and date the indicated places on the CRF. These signatures will indicate that the principal Investigator inspected or reviewed the data on the CRF, the data queries, and the Study Center notifications, and agrees with the content.

12.5 Language

Case report forms must be completed in English. Generic names for concomitant medications should be recorded in English if possible, unless it is a combination drug, then record the trade name in English.

All written information and other material to be used by patients and investigative staff must use vocabulary and language that are clearly understood.

12.6 Compensation for Injury

The Sponsor maintains appropriate insurance coverage for clinical trials and will follow applicable local compensation laws. Patients will be treated and/or compensated for any study-related illness/injury in accordance with the information provided in the Compensation for Injury section of the Informed Consent document.

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14. APPENDICES

Appendix A Schedule of Procedures

Screen/Run In through Treatment Period

Post-Treatment Follow-up

Appendix A Schedule of Procedures – Screen/Run In through Treatment Period

Study Period		Screen/ Run In[a]	Qual[a]	Treatment Period																							
Study Week		-8 to -2	-2 to -1	Wk 1		Wk 2.5	Wk 4	Wk 6	Wk 8	Wk 10	Month 3		Wk 15 & 17	Wk 19	Wk 21 & 23	Month 6		Wk 28 & 30	Wk 32	Wk 34 & 36	Wk 38	Wk 40 & 42	Wk 44	Wk 46 & 48	Month 12	
											Wk 12	Wk 13				Wk 25	Wk 26								Wk 50	Wk 52 or ET
Study Day		-56 to -15	-14 to -7	1	2	11	22	36	50	64	78	85	99 & 113	127	141 & 155	169	176	190 & 204	218	232 & 246	260	274 & 288	302	316 & 330	344	358
Visit Window+/- Days		0	0	0	0	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Informed Consent		X	X																							
Outpatient Visit		X	X	X	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X	X[l]	X[l]	X[l]	X[l]	X	X[l]	X[l]	X[l]	X	X[l]	X[l]	X[l]	X[l]	X
Inclusion/Exclusion Criteria		X	X																							
Vital Signs + body weight (+ height on Day 1 only)		X	X	X			X		X			X					X				X					X
Physical Examination		X	X	X								X					X				X					X
12- lead ECG (triplicate)		X	X									X					X				X					X
MRI (liver/spleen)		X																								X[k]
Echocardiography		X															X[k]									X[k]
Blood Draw (Fasting)[c]	Chemistry Panel	X	X	X			X		X			X		X			X		X		X		X			X
	CBC with Differential[b]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Serum Lipid Panel	X	X	X			X		X		X	X				X	X				X				X	X
	Coagulation (aPTT, PT, INR)	X	X						X			X					X				X					X
	hsCRP, HbA1c, FPG, and de-lipidated free glycerol	X[n]	X[n]	X								X					X									X
	Sedimentation Rate			X								X					X									X
	Complement (C5a, Bb)			X								X					X									X
	Plasma PK - Volanesorsen			X[l]	X		X		X			X					X				X					X
	Anti-Volanesorsen Antibodies			X			X		X			X					X				X					X
	FSH (women only, if applicable)	X	X																							
	Serum Pregnancy Test[d]	X	X				X		X			X		X			X		X		X		X			X
	Archived Serum & Plasma Samples[e]			X					X			X					X									X
	Troponin I[o]	X	X																							

Appendix A Schedule of Procedures - Screen/Run In through Treatment Period *Continued*

Study Period	Screen/ Run In[a]	Qual[a]	Treatment Period																								
Study Week	-8 to -2	-2 to -1	Wk 1		Wk 2.5	Wk 4	Wk 6	Wk 8	Wk 10	Month 3		Wk 15 & 17	Wk 19	Wk 21 & 23	Month 6		Wk 28 & 30	Wk 32	Wk 34 & 36	Wk 38	Wk 40 & 42	Wk 44	Wk 46 & 48	Month 12	
										Wk 12	Wk 13				Wk 25	Wk 26								Wk 50	Wk 52 or ET
Study Day	-56 to -15	-14 to -7	1	2	11	22	36	50	64	78	85	99 & 113	127	141 & 155	169	176	190 & 204	218	232 & 246	260	274 & 288	302	316 & 330	344	358
Visit Window+/- Days	0	0	0	0	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Urinalysis[c]	X	X	X[m]			X		X			X[m]		X[m]			X[m]		X[m]		X[m]		X[m]			X[m]
Fundus Photography[f]	X																								X[k]
Genetic testing for FCS diagnosis (if not available in medical history)[g]	X																								
Weekly Study Drug: SC Injection			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Symptom Diary (weekly)	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Assessment(s)			X								X					X									X
Food/Drink Diary (quarterly)[h]			X								X					X									X
Diet/Alcohol Counseling[i]	X	X	X			X		X			X					X				X					X
Adverse Events	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Appendix A Schedule of Procedures – Post-Treatment Follow-up

Study Period		Post Treatment Follow-up[p]				
Study Week		Wk 54 & 56	Wk 58	Wk 65	Wk 71	Wk 78
Study Day		372 & 386	400	449	491	540
Visit Window+/- Days		2	7	7	7	7
Informed Consent						
Outpatient Visit		X[l]	X[l]	X	X[l]	X
Inclusion/Exclusion Criteria						
Vital Signs + body weight (+ height on Day 1 only)				X		X
Physical Examination				X		X
12- lead ECG (triplicate)				X		X
MRI (liver/spleen)						
Echocardiography						
Blood Draw (Fasting)[c]	Chemistry Panel		X	X	X	X
	CBC with Differential[b]	X	X	X	X	X
	Serum Lipid Panel			X		X
	Coagulation (aPTT, PT, INR)					
	hsCRP, HbA1c, FPG, and de-lipidated free glycerol			X		X
	Sedimentation Rate			X		X
	Complement (C5a, Bb)			X		X
	Plasma PK - Volanesorsen			X		X
	Anti-Volanesorsen Antibodies			X		X
	FSH (women only, if applicable)					
	Serum Pregnancy Test[d]		X	X	X	X
	Archived Serum & Plasma Samples[e]			X		X
	Troponin I[o]					

Appendix A Schedule of Procedures – Post-Treatment Follow-up *Continued*

Study Period	Post Treatment Follow-up[p]				
Study Week	**Wk 54 & 56**	**Wk 58**	**Wk 65**	**Wk 71**	**Wk 78**
Study Day	**372 & 386**	**400**	**449**	**491**	**540**
Visit Window+/- Days	**2**	**7**	**7**	**7**	**7**
Urinalysis[c]		X[m]	X[m]	X[m]	X[m]
Fundus Photography[f]					
Genetic testing for FCS diagnosis (if not available in medical history)[g]					
Weekly Study Drug: SC Injection					
Symptom Diary (weekly)	X	X	X	X	X
Quality of Life Assessment(s)			X		X
Food/Drink Diary (quarterly)[h]			X		X
Diet/Alcohol Counseling[i]		X	X	X	X
Adverse Events	X	X	X	X	X
Concomitant Medication	X	X	X	X	X

Appendix A Schedule of Procedures *Continued*

a Screening (Group 3) and Qualification procedures performed (Please refer to Sections 3.4, 4.1, and 6.1.2)

b Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1-week and determined not to have met a stopping rule before dosing can continue. If there is no reportable platelet count within 14 days of the last platelet count, the Investigator will contact the patient to hold dosing until a new platelet count is obtained and reviewed. All platelet count results will be promptly reviewed by the Investigator to ensure that the count has not met the stopping rule and to determine whether the rate of decline is suggestive that the patient could be approaching the dose pause rule of 75,000/mm^3. In the event of any platelet count less than 50,000/mm^3 or a rate of decline ≥ 50% between two consecutive assessments, irrespective of the platelet level, then dosing of a patient with Study Drug (ISIS 304801 or placebo) will be stopped permanently. Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor

c Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours. During treatment period urine and blood samples will be collected prior to Study Drug administration. Does not apply to 24-hour PK blood draw

d Females of childbearing potential only

e Serum and plasma samples will be collected and stored for follow-up exploration of laboratory findings and/or adverse events (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.) in this or subsequent clinical studies of volanesorsen

f If possible, fundus photography should be completed prior to administration of the first dose of Study Drug (Group 2 [ISIS 304801-CS16 rollover patients] and Group 3) and repeated at Week 52 (Please refer to Section 6.2.2.2)

g Genetic testing can be conducted for study qualification (Group 2 [ISIS 304801-CS16 rollover patients] and Group 3); genetic testing will only be conducted if allowed in the geographic region and only after the patient has given specific written informed consent for genetic testing

h In addition to diary, patients will be contacted at random times during the study to review their current eating and drinking habits

i To reinforce compliance to the diet and alcohol restrictions. Random diet/alcohol assessments (phone visits) will also be performed by dietician or study personnel

j Assessments and procedures to be conducted by either a home healthcare nurse, or the Study Center as arranged by the Study Center personnel

k A ± 7-day window is allowed for MRI, echocardiography procedures and fundus photography

l Full or abbreviated PK profile (see Appendix C)

m Expanded urinalysis (see Appendix B)

n HbA1c only

o All abnormal troponin samples will be rerun at the central laboratory and also analyzed for CK-MB

p If needed, the post-treatment follow-up period will be extended (with patients monitored every 6 weeks) until apoC-III levels return to baseline values

Appendix B List of Laboratory Analytes

Appendix B List of Laboratory Analytes

Based on emerging data from this or future studies, additional tests not listed below may be performed on stored samples to better characterize the profile of volanesorsen or other similar oligonucleotides.

Clinical Chemistry Panel

- Sodium
- Potassium
- Chloride
- Bicarbonate
- Total protein
- Albumin
- Calcium
- Magnesium
- Phosphorus
- Glucose
- BUN
- Creatinine
- Uric Acid
- Total bilirubin
- Direct (conjugated) bilirubin
- Indirect (unconjugated) bilirubin
- ALT
- AST
- Alkaline phosphatase

Coagulation

- aPTT (sec)
- PT (sec)
- INR

Lipid Panel

- Total Cholesterol
- LDL-C
- HDL-C
- Triglycerides
- Non-HDL-C
- VLDL-C
- apoA-1
- apoB
- apoC-III

Hematology

- Red blood cells
- Hemoglobin
- Hematocrit
- MCV, MCH, MCHC
- Platelets
- White blood cells
- WBC Differential (% and absolute)
  - Neutrophils
  - Eosinophils
  - Basophils
  - Lymphocytes
  - Monocytes

Pharmacokinetics[1] & Immunogenicity

- Volanesorsen levels in plasma
- Anti-volanesorsen antibodies in plasma

Other Assessments

- hsCRP
- Sedimentation Rate
- C5a, Bb
- De-lipidated free glycerol
- HbA1c, FPG

Urinalysis

- Color
- Appearance
- Specific gravity
- pH
- Protein
- Blood
- Ketones
- Urobilinogen
- Glucose
- Bilirubin
- Leukocyte esterase
- Nitrate
- Microscopic examination[2]

Additional Measures for Expanded Urinalysis

- Total protein (quantitative)
- Microalbumin
- β2-microglobulin

1 Plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, IM testing (or possibly for purposes of IM assay development and/or validation), or to assess other actions of volanesorsen with plasma constituents

2 Will be performed on abnormal findings unless otherwise specified

Appendix C Pharmacokinetic Sampling Schedule

Appendix C Pharmacokinetic Sampling Schedule

Blood samples for the determination of plasma volanesorsen concentrations will be collected prior to dosing, and at various times throughout the dosing and post-treatment follow-up period as noted in the tables below.

PK Sampling Schedule (All Patients except PK Subgroup)

Week	Wk 1	Wk 4	Wk 8	Wk 13	Wk 26	Wk 38	Wk 52	Wk 65	Wk 78
Study Day	D1	D22	D50	D85	D176	D260	D358	D449	D540
Visit Window +/- Days	0	2	2	2	2	3	2	7	7
Time Point	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime	Anytime

PK Sampling Schedule (PK Subgroup only*)

Week	Wk 1	Wk 1	Wk 4	Wk 8	Wk 13	Wk 26	Wk 38	Wk 52	Wk 65	Wk 78
Study Day	D1	D2	D22	D50	D85	D176	D260	D358	D449	D540
Visit Window +/- Days	0	0	2	2	2	2	3	2	7	7
Time Point	Pre-dose, 1, 2, 3, 4, 6, 8, and 12 hrs post-dose	24 hrs post-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime	Anytime

* Patients at selected sites will be asked to participate in the extended 24-hour PK profile beginning on Study Day 1. Participation is optional

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

The following grading recommendations for adverse events relating to lab test abnormalities are based upon the **Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010**

Adverse Event	Mild	Moderate	Severe
Hematology			
aPTT prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage
Eosinophils increased†	650 – 1,500 cell/mm^3	1,501 - 5,000 cell/mm^3	>5,000 cell/mm^3
Fibrinogen decreased	<1.0 - 0.75 x LLN or <25% decrease from baseline	<0.75 - 0.5 x LLN or 25 - <50% decrease from baseline	<0.5 x LLN or ≥50% decrease from baseline
Hemoglobin decreased (Anemia)	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated
Hemoglobin increased	Increase in >0 - 2 g/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 g/dL above ULN or above baseline if baseline is above ULN	Increase in >4 g/dL above ULN or above baseline if baseline is above ULN
INR increased	>1 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation
Lymphocyte count decreased	<LLN - 800/mm^3; <LLN - 0.8 x 10^9/L	<800 - 500/mm^3; <0.8 - 0.5 x 10^9 /L	<500 /mm^3; <0.5 x 10^9 /L
Lymphocyte count increased	-	>4000/mm^3 - 20,000/mm^3	>20,000/mm^3
Neutrophil count decreased	<LLN - 1500/mm^3; <LLN - 1.5 x 10^9 /L	<1500 - 1000/mm^3; <1.5 - 1.0 x 10^9 /L	<1000/mm^3; <1.0 x 10^9 /L
Platelet count decreased	<LLN - 75,000/mm^3; <LLN - 75.0 x 10^9 /L	<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9 /L	<50,000/mm^3; <50.0 x 10^9 /L
White blood cell decreased	<LLN - 3000/mm^3; <LLN - 3.0 x 10^9 /L	<3000 - 2000/mm^3; <3.0 - 2.0 x 10^9 /L	<2000/mm^3; <2.0 x 10^9 /L
Chemistry			
Acidosis	pH <normal, but >=7.3	-	pH <7.3
Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Alkalosis	pH >normal, but ≤7.5	-	pH >7.5
Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 x ULN
Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

Adverse Event	Mild	Moderate	Severe
Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer
CD4 lymphocytes decreased	<LLN - 500/mm^3; <LLN - 0.5 x 10^9 /L	<500 - 200/mm^3; <0.5 - 0.2 x 10^9 /L	<200/mm^3; <0.2 x 10^9 /L
CPK increased*	>ULN - <6 ULN	6 - 10 x ULN	>10 x ULN
Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 x ULN
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 mg/dL; >3.1 mmol/L; Ionized calcium >1.6 mmol/L; hospitalization indicated
Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 mg/dL; >13.9 mmol/L; hospitalization indicated
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0; hospitalization indicated
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 mg/dL; >1.23 mmol/L
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 mmol/L; hospitalization indicated
Hyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 mg/dL; <1.75 mmol/L; Ionized calcium <0.9 mmol/L; hospitalization indicated
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 mg/dL; <3.0 mmol/L	<40 mg/dL (<2.2 mmol/L) AND requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions‡
Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 mmol/L; hospitalization indicated
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 mg/dL; <0.4 mmol/L
Hyponatremia	<LLN - 130 mmol/L	-	<130 mmol/L
Hypophosphatemia	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 mg/dL; <0.6 mmol/L
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

Adverse Event	Mild	Moderate	Severe
Urine			
Proteinuria Adults Children	1+ proteinuria; urinary protein <1.0 g/24 hrs -	2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs; Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Urinary protein ≥3.5 g/24 hrs; Urine P/C >1.9
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated

†Grading for this parameter is derived from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007

*Grading for this parameter is derived from the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0, Nov 2014

‡Modified for consistency with the ADA and Endocrine Society Guidelines (Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. Diabetes Care 2013;36:1384-95)

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ISIS 304801-CS7

The APPROACH Open-Label Study

Volanesorsen (ISIS 304801)

An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol Amendment 5 - France – 19 August 2016

EudraCT No: 2015-003755-21

ISIS 304801-CS7

The APPROACH Open-Label Study

Volanesorsen (ISIS 304801)

An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol Amendment 5 - France – 19 August 2016

Protocol History:

Original Protocol:	28 August 2015
Protocol Amendment 1:	2 February 2016
Protocol Amendment 2:	22 April 2016
Protocol Amendment 3:	9 May 2016
Protocol Amendment 4:	6 June 2016

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Ionis Protocol Number: ISIS 304801-CS7

Protocol Amendment 5 - France

EudraCT No: 2015-003755-21

Clinical Phase: 3

The APPROACH Open-Label Study

Volanesorsen (ISIS 304801)

An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

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Date: 19 August 2016

Confidentiality Statement

This document contains confidential information of Ionis Pharmaceuticals, Inc., that must not be disclosed to anyone other than the recipient study staff and members of the independent ethics committee, institutional review board, or authorized regulatory agencies. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc.

Protocol Signature Page

Protocol Number:	ISIS 304801-CS7
Protocol Title:	An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Amendment:	Amendment 5 - France
Date:	19 August 2016

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)", dated 19 August 2016, and agree to conduct the study as described herein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice (E6).

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc.

Investigator's Signature

Investigator's Name *(please print)*

Date (DD Month YYYY)

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PROTOCOL AMENDMENT

Protocol Number:	ISIS 304801-CS7
Protocol Title:	An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Amendment Number:	5 - France
Amendment Date:	19 August 2016

The purpose of this protocol amendment is to implement the following modifications to Protocol ISIS 304801-CS7 Amendment 4 dated 6 June 2016:

1. To enroll FCS patients in this open-label study who did not participate in the ISIS 304801–CS6 or ISIS 304801–CS16 index studies.

   For clarity, the protocol now specifies 3 patient groups, with assignment based on prior involvement in index studies of ISIS 304801:

   Group 1: ISIS 304801-CS6 (index study) rollover FCS patients

   Group 2: ISIS 304801-CS16 (index study) rollover FCS patients

   Group 3: FCS patients who did not participate in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies

2. To remove language that indicates that lipoprotein lipase (LPL) activity can be measured if needed for study qualification for patients in Groups 2 and 3.

3. To add language to indicate that a second Study Drug rechallenge will not be allowed following a platelet count decrease below 75,000/mm^3.

4. To provide clarifications to the platelet safety monitoring rules in Table 2.

5. To add language to indicate that patients who discontinue early from Study Drug, or the study, should be followed as per the platelet monitoring rules shown in Table 2 for the first 6 weeks after discontinuing Study Drug and the next platelet count should be taken within at least 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug.

6. Following guidance provided by the ANSM

   a. Following guidance provided by the ANSM, the complete stop of Study Drug in patients whose platelet threshold is below 25,000/mm^3 will be changed to below 50,000/mm^3

b. To add a criteria for treatment discontinuation: patient participation to the trial must be stopped if a decrease in platelets greater than or equal to 50% between two consecutive assessments is observed, irrespective of the platelet level

c. To add in the footnote to Appendix A that in the event of any platelet count less than 50,000/mm^3 or a rate of decline ≥ 50% between two consecutive assessments, irrespective of the platelet level, then dosing of a patient with Study Drug (ISIS 304801 or placebo) will be stopped permanently

d. To add in the Exclusion Criteria patients that already had thrombocytopenia

e. To add language to exclude patients that meet the Exclusion Criteria of their index study

Minor changes (not included in the list of changes below) have been made throughout the protocol to correct errors and/or to improve the overall clarity of the original protocol but these changes do not impact subject safety, exposure, or the overall study design.

The following table provides a summary list of major changes to the protocol:

Protocol Section	Description of Change	Rationale
Protocol Title pages Signature page Protocol Synopsis: Title, Study Population, Rationale for Dose and Schedule Selection, Study Visit Schedule and Procedures, Statistical Considerations 5.1 Inclusion Criteria	"Extension" was removed from the study title.	To note that FCS patients who did not participate in an index study will also be enrolled.
Protocol Synopsis: Study Design 3.1 Study Design	**Was:** This is a multi-center open-label extension study of ISIS 304801-CS6 and ISIS 304801-CS16 **Is:** This is a multi-center open-label study of: Group 1: ISIS 304801-CS6 (index study) roll over FCS patients Group 2: ISIS 304801-CS16 (index study) roll over FCS patients Group 3: FCS patients who did not participate in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies	To distinguish patients who participated in an index study from those who did not.

Protocol Section	Description of Change	Rationale
Protocol Synopsis: Study Population 5.1 Inclusion Criteria	Inclusion Criteria **Was:** 3. Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement. Patients who are enrolled in ISIS 304801-CS16 must also meet the following criteria in order to enter into the Extension Study: a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L) b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) by documentation of at least 1 of the following: • Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1) • Post heparin plasma LPL activity of ≤ 20% of normal c. Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 study **Is:** 3. Groups 1 and 2: Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement. Groups 2 and 3: Patients must also meet the following criteria in order to enter into the open-label study: a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L) b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) by documentation of the following: • Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1) c. Group 2: Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 index study Group 3: Fasting TG ≥ 750 mg/dL at Screening for this open-label study	To define the inclusion criteria for each Group of patients. LPL removed to avoid the production of heparin induced anti-platelet antibodies.

Protocol Section	Description of Change	Rationale
Protocol Synopsis: Study Population 5.2 Exclusion Criteria	Exclusion Criteria **Was:** 1. Have any new condition or worsening of existing condition which in the opinion of the Investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study 2. Unwilling to comply with lifestyle requirements for the duration of the study (Section 6.3) **Is:** **Exclusion Criteria** 1. Diabetes mellitus with any of the following: a. Newly diagnosed within 12 weeks of screening* b. HbA1c ≥ 9.0% at Screening* c. Recent change in anti-diabetic pharmacotherapy (change in dosage or addition of new medication within 12 weeks of screening* [with the exception of ± 10 units of insulin]) d. Anticipated need to change dose or type of medication during the treatment period of the Study [with the exception of ± 10 units of insulin] e. Current use of GLP-1 agonists 2. Severe hypertriglyceridemia other than due to familial chylomicronemia syndrome 3. Active pancreatitis within 4 weeks prior to screening* 4. History within 6 months of screening* of acute or unstable cardiac ischemia (myocardial infarction, acute coronary syndrome, new onset angina), stroke, transient ischemic attack or unstable congestive cardiac failure requiring a change in medication or major surgery within 3 months of screening* 5. Any of the following laboratory values at Screening* a. Hepatic: • Total bilirubin > upper limit of normal (ULN), unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL • ALT > 2.0 x ULN • AST > 2.0 x ULN b. Renal: • Persistently positive (2 out of 3 consecutive tests ≥ 1+) for protein on urine dipstick. In the event of a positive test eligibility may be confirmed by a quantitative total urine protein measurement of < 500 mg/24 hrs • Persistently positive (2 out of 3 consecutive tests ≥ trace positive) for blood on urine dipstick. In the event of a positive test eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field • Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault < 50 mL/min (MDRD or CKD-EPI formulas can be used instead of Cockcroft-Gault for estimation of GFR in patients with low body weight after discussion with Sponsor Medical Monitor)	To define the exclusion criteria for each Group of patients and to make the eligibility criteria for the Group 3 patients consistent with those for the Group 1 index study patients.

Protocol Section	Description of Change	Rationale
Protocol Synopsis: Study Population *Continued* 5.2 Exclusion Criteria *Continued*	Exclusion Criteria **Is:** ***Continued*** c. Cardiac Troponin I > ULN at Screening* d. LDL-C > 130 mg/dL at Screening* e. Any other laboratory abnormalities which, in the opinion of the Investigator or the Sponsor, would make the patient unsuitable for inclusion 6. Uncontrolled hypertension (BP > 160/100 mm Hg) 7. History of thrombocytopenia (platelet count < 100,000/mm^3) or bleeding diathesis or coagulopathy or clinically-significant abnormality in coagulation parameters at Screening* 8. History of heart failure with NYHA greater than Class II 9. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1 10. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B 11. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated 12. Treatment with another investigational drug, biological agent, or device within 1-month of screening*, or 5 half-lives of investigational agent, whichever is longer 13. Unwilling to comply with lifestyle requirements (Section 6.3) 14. Use of any of the following: a. Statins, omega-3 fatty acids (prescription and OTC), or fibrates unless on a stable dose for at least 3 months prior to screening* and dose and regimen expected to remain constant during the treatment period. Patients taking OTC omega-3 fatty acids should make every effort to remain on the same brand throughout the study b. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to screening* c. Systemic corticosteroids or anabolic steroids within 6 weeks prior to screening* unless approved by the Sponsor Medical Monitor d. Atypical antipsychotic medications (e.g., olanzapine and clozapine) unless on a stable dose for at least 3 months prior to screening* and dose and regimen expected to remain stable throughout the study e. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to screening* and dose and regimen expected to remain constant during the treatment period f. Glybera gene therapy within 2 years prior to screening* g. Oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, and apixaban) unless on a stable dose for at least 4 weeks prior to screening* and regular clinical monitoring is performed h. Tamoxifen, estrogens or progestins unless on a stable dose for at least 4 months prior to screening* and dose and regimen expected to remain constant during the treatment period i. Plasma apheresis within 4 weeks prior to screening* or planned during the study	To define the exclusion criteria for each Group of patients and to make the eligibility criteria for the Group 3 patients consistent with those for the Group 1 index study patients. *Continued*

Protocol Section	Description of Change	Rationale
Protocol Synopsis: Study Population *Continued* 5.2 Exclusion Criteria *Continued*	Exclusion Criteria **Is:** ***Continued*** j. Prior exposure to ISIS 304801 k. Any other medication unless stable at least 4 weeks prior to screening* (Occasional or intermittent use of over-the-counter medications will be allowed at Investigator's discretion) 15. Blood donation of 50 to 499 mL within 30 days of screening* or of > 499 mL within 60 days of screening* 16. Known hypersensitivity to any of the excipients of the Study Drug (ISIS 304801 or placebo) 17. Have any other conditions, including new or worsening of existing condition, which, in the opinion of the Investigator or the Sponsor would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the study *(Group 3) or Qualification (Groups 1 and 2)	To define the exclusion criteria for each Group of patients and to make the eligibility criteria for the Group 3 patients consistent with those for the Group 1 index study patients.
Protocol Synopsis: Study Visit Schedule and Procedures 3.4 Overall Study Duration and Follow-up Appendix A	**Was:** The study for an individual patient will generally consist of the following periods: A qualification period of up to 2 weeks (unless approved by the Sponsor). Please refer to Section 4.1 and Appendix A. ○ A 52-week treatment period during which volanesorsen will be administered as a once weekly SC injection ○ A 13-week post-treatment evaluation period **Is:** The study for an individual patient will generally consist of the following periods: • Group 1 and 2 patients (participated in ISIS 304801-CS6 or ISIS 304801-CS16 index study): A qualification period of up to 2 weeks (unless approved by the Sponsor). Please refer to Section 4.1 and Appendix A. • Group 3 patients (did not participate in an index study): An up to 8-week screening and qualification period, including a diet stabilization period of at least 6 weeks (screening and diet stabilization period may be reduced, per Sponsor approval, if the patient is following a diet for optimal control of TGs and disease management prior to screening). Please refer to Section 6.1.2 and Appendix A. • All patients: ○ A 52-week treatment period during which volanesorsen will be administered as a once weekly SC injection ○ A 13-week post-treatment evaluation period	To distinguish the Screening/ Qualification period for patients who participated in an index study from those who did not.
4.1 Screening/Qualification	Group 3 (Screening and Qualification): At the time of consent, the patient will be considered enrolled into the study and will be assigned a unique screening number before any study procedures, including screening procedures, are performed. At the time of enrollment, patients will be assigned a unique patient identification number. This number will be used to identify the patient throughout the trial and must be used on all study documentation related to that patient. The screening number and patient identification number must remain constant throughout the entire trial. In the event the patient is re-consented and re-screened the patient must be given a new screening number. Screening numbers and patient identification numbers, once assigned, will not be re-used	To define the enrollment criteria for patients who did not participate in an index study.

<table>
<tr><th>Protocol Section</th><th>Description of Change</th><th>Rationale</th></tr>
<tr><td>6.1.2 Screening and Qualification (Group 3)</td><td>Before any study-specific procedures or evaluations are initiated, patients must sign and date the informed consent form. An 8-week period, including a diet stabilization period of at least 6 weeks (screening and diet stabilization period may be reduced, per Sponsor approval, if the patient is following a diet for optimal control of TGs and disease management prior to screening) is given to perform the screening evaluations. The qualification assessments will be performed at Week -2 to -1, ideally after patient eligibility has been determined, and on Study Day 1. Abnormal screening results may be retested for review by the Study Medical Monitor for eligibility purposes</td><td>To define the Screening and Qualification procedures for patients who did not participate in an index study.</td></tr>
<tr><td>8.6.3 Stopping Rules for Platelet Count Results</td><td><u>Was:</u>
If after the first dosing rechallenge the platelet count again falls below 75,000/mm^3, then dosing of the patient must be held until the platelet count again returns to at least 100,000/mm^3. The suitability of the patient for continued dosing and the need for any further modification to treatment schedule or dose (refer to Section 8.7) will be re-examined by the Investigator in consultation with the Study Medical Monitor based on (at least) the factors mentioned above.
If after the second rechallenge the platelet count falls below 75,000/mm^3 and is subsequently confirmed (see Section 8.5), dosing with volanesorsen will be stopped permanently. The follow-up schedule for any events meeting this stopping criterion will be determined by the Investigator in consultation with the Study Medical Monitor.

<u>Is:</u>
If after the first dosing rechallenge the platelet count again falls below 75,000/mm^3, then dosing of the patient with Study Drug will be stopped permanently.</td><td>Text was removed as a second Study Drug rechallenge will not be allowed following a platelet count decrease below 75,000/mm^3.</td></tr>
<tr><td>8.6.3 Stopping Rules for Platelet Count Results
Table 2 Actions in Patients with Low Platelet Count</td><td>
<table>
<tr><th>Platelet Count on Rx</th><th>Drug Dose</th><th>Monitoring</th></tr>
<tr><td>Normal range, > 140K/mm^3</td><td>No action</td><td>Monitor every 2 weeks</td></tr>
<tr><td>100K-140K/mm^3</td><td>No action</td><td>Closer observation
Monitor every 1-week <u>until stable*</u></td></tr>
<tr><td>75K-100K/mm^3</td><td><u>Permanently</u> reduce dose frequency to 300mg every 2 weeks or reduce dose to 150 mg weekly</td><td>Closer observation
Monitor every 1-week</td></tr>
</table>
</td><td>To provide clarification to the platelet safety monitoring rules.

Note: Changes are reflected as bold underlined text.</td></tr>
</table>

<table>
<tr><th>Protocol Section</th><th>Description of Change</th><th>Rationale</th></tr>
<tr><td>8.6.3 Stopping Rules for Platelet Count Results
Table 2 Actions in Patients with Low Platelet Count
Continued</td><td>
<table>
<tr><th>Platelet Count on Rx</th><th>Drug Dose</th><th>Monitoring</th></tr>
<tr><td>50K-75K/mm^3</td><td><u>If occurs while on dose of 300 mg every 2 weeks or 150 mg every week then permanently discontinue Study Drug, otherwise dose pause.</u>
<u><s>Dose pause</s></u>
When platelet count returns to > 100K/mm^3 restart dosing at dose frequency of 300 mg every 2 weeks or 150 mg weekly only if approved by Sponsor Medical Monitor</td><td>Closer observation
Monitor every 2-3 days until 2 successive values show improvement
Consider discontinuation of antiplatelet agents/NSAIDS/ anticoagulant medication</td></tr>
<tr><td>25K-50K/mm^3 or a rate of decline ≥ 50% between 2 consecutive assessments, irrespective of the platelet level</td><td>Permanently discontinue Study Drug</td><td>Closer observation
Monitor daily until 2 successive values show improvement then monitor every 2 3 days until platelet count stable
Discontinue antiplatelet agents/NSAIDS/anticoagulant medication while platelet count < 50K/mm^3 if possible</td></tr>
</table>
</td><td>To provide clarification to the platelet safety monitoring rules

Note: Changes are reflected as bold underlined text</td></tr>
</table>

<table>
<tr><th>Protocol Section</th><th>Description of Change</th><th>Rationale</th></tr>
<tr><td>8.6.3 Stopping Rules for Platelet Count Results
Table 2 Actions in Patients with Low Platelet Count
Continued</td><td>
<table>
<tr><td>< 25K/mm^3</td><td>Permanently discontinue Study Drug</td><td>Closer observation:
Monitor daily until 2 successive values show improvement then monitor every 2-3 days until platelet count stable
Steroids recommended**
Consider need for hospitalization and referral to hematologist
Discontinue antiplatelet agents/NSAIDS/anticoagulant medication while platelet count < 50K/mm^3 if possible</td></tr>
</table>
* <u>At least 3 consecutive values measured weekly that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3</u>
** Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (note: may require continuation with oral steroids after methyl prednisolone)</td><td>To provide clarification to the platelet safety monitoring rules

Note: Changes are reflected as bold underlined text</td></tr>
<tr><td>8.8.1 Follow-up Visits for Early Termination from Treatment Period</td><td><u>Was:</u>
Any patient who discontinues early from the Treatment Period should be strongly encouraged to attend applicable landmark visits at Weeks 2, 13, 25, 26, and 51, 52 (calculated based on the time elapsed since Day 1) to collect fasting lipid panels and conduct safety assessments in accordance with the schedule of procedures in Appendix A. Any patient who discontinues treatment after Week 44 should also be strongly encouraged to attend a final follow-up visit (Week 65 visit assessments) approximately 13 weeks after their last dose of Study Drug, in addition to the applicable landmark visits.</td><td>To provide guidance to the platelet safety monitoring rules for patients that discontinue early from the Treatment Period.</td></tr>
</table>

Protocol Section	Description of Change	Rationale
8.8.1 Follow-up Visits for Early Termination from Treatment Period *Continued*	**Is:** Any patient who discontinues early from the Treatment Period should be followed as per the platelet monitoring rules shown in Table 2 in Section 8.6.3 for the first 6 weeks after discontinuing Study Drug. Following this period, if the platelet count is stable (at least 3 consecutive values that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3), the next platelet count should be taken within at least 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug. Patients should also be strongly encouraged to attend applicable landmark visits at Weeks 12, 13, 25, 26, and 50, 52 (calculated based on the time elapsed since Day 1) to collect fasting lipid panels and conduct safety assessments in accordance with the schedule of procedures in Appendix A. Any patient who discontinues treatment after Week 44 should also be strongly encouraged to attend a final follow-up visit (Week 65 visit assessments) approximately 13 weeks after their last dose of Study Drug, in addition to the applicable landmark visits.	To provide guidance to the platelet safety monitoring rules for patients that discontinue early from the Treatment Period.
8.8.2 Follow-up Visits for Early Termination from Post-Treatment Follow-up Period	**Was:** The patient who requests to withdraw from the study during the Post-Treatment Follow-up Period should be encouraged to undergo a final follow-up visit (Week 65, see Appendix A) prior to leaving the study. **Is:** The patient who requests to withdraw from the study during the Post-Treatment Follow-up Period should be encouraged to follow the platelet monitoring rules shown in Table 2 in Section 8.6.3 for the first 6 weeks after discontinuing Study Drug. Following this period, if the platelet count is stable (at least 3 consecutive values that are stable as determined by the Sponsor medical monitor and > 100,000/mm^3), the next platelet count should be taken within at least 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug. Patients should also be encouraged to undergo a final follow-up visit (Week 65, see Appendix A) prior to leaving the study.	To provide guidance to the platelet safety monitoring rules for patients that discontinue early from the Post-Treatment Follow-up Period.
8.6.3 Stopping Rules for Platelet Count Results Table 2 Actions in Patients with Low Platelet Count	**Was:** In the event of any platelet count less than 25,000/mm^3, or a platelet count less than 75,000/mm^3 that occurs while the patient is on dosing at 300 mg every 2 weeks or 150 mg every week, then dosing of a patient with volanesorsen will be stopped permanently. **Is:** In the event of any platelet count less than 50,000/mm^3, or a rate of decline ≥ 50% between two consecutive assessments, irrespective of the platelet level, then dosing of a patient with volanesorsen will be stopped permanently**.**	To follow guidance provided by the ANSM to provide additional patient safety regarding platelet stopping rules.
Appendix A	**Added to Footnote "b":** In the event of any platelet count less than 50,000/mm^3 or a rate of decline ≥ 50% between two consecutive assessments, irrespective of the platelet level, then dosing of a patient with Study Drug (ISIS 304801 or placebo) will be stopped permanently.	To follow guidance provided by the ANSM to clarify the additional patient safety regarding platelet stopping rules in Appendix A.

Protocol Section	Description of Change	Rationale
Protocol Synopsis: Study Population 5.2 Exclusion Criteria	Exclusion Criteria **Was:** 7. History of bleeding diathesis or coagulopathy or clinically-significant abnormality in coagulation parameters at Screening **Is:** 7. History of thrombocytopenia (platelet count < 100,000/mm^3) or bleeding diathesis or coagulopathy or clinically-significant abnormality in coagulation parameters at Screening	To exclude patients with a history of thrombocytopenia because it sometimes seems to be associated with patients suffering from hyperchylomicronemia

PROTOCOL SYNOPSIS

Protocol Title	An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Study Phase	3
Indication	Familial Chylomicronemia Syndrome
Study Objectives	To evaluate the safety and efficacy of dosing and extended dosing with volanesorsen (volanesorsen sodium 300 mg) in patients with FCS
Study Design	This is a multi-center open-label study of: Group 1: ISIS 304801-CS6 (index study) roll over FCS patients Group 2: ISIS 304801-CS16 (index study) roll over FCS patients Group 3: FCS patients who did not participate in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies All patients will receive volanesorsen 300 mg once per week for 52 weeks. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period. Following the Week 52 visit, patients will enter a 13-week post-treatment evaluation period.
Number of Patients	Up to approximately 70 patients dosed
Study Population	<u>Inclusion Criteria:</u> 1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law 2. Age ≥ 18 years at time of informed consent 3. Groups 1 and 2: Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement. Groups 2 and 3: Patients must also meet the following criteria in order to enter into the open-label study: a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L) b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) by documentation of the following: • Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1) c. Group 2: Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 index study Group 3: Fasting TG ≥ 750 mg/dL at Screening for this open-label study 4. Able and willing to participate in a 65-week study

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	Inclusion Criteria: *Continued* 5. Satisfy 1 of the following: a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved), abstinent*, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration b. Males: Surgically sterile, abstinent* or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration * Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception Exclusion Criteria 1. Diabetes mellitus with any of the following: a. Newly diagnosed within 12 weeks of screening* b. HbA1c ≥ 9.0% at Screening* c. Recent change in anti-diabetic pharmacotherapy (change in dosage or addition of new medication within 12 weeks of screening* [with the exception of ± 10 units of insulin]) d. Anticipated need to change dose or type of medication during the treatment period of the Study (with the exception of ± 10 units of insulin) e. Current use of GLP-1 agonists 2. Severe hypertriglyceridemia other than due to familial chylomicronemia syndrome 3. Active pancreatitis within 4 weeks prior to screening* 4. History within 6 months of screening* of acute or unstable cardiac ischemia (myocardial infarction, acute coronary syndrome, new onset angina), stroke, transient ischemic attack or unstable congestive cardiac failure requiring a change in medication or major surgery within 3 months of screening*

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	Exclusion Criteria *Continued* 5. Any of the following laboratory values at Screening* a. Hepatic: • Total bilirubin > upper limit of normal (ULN), unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL • ALT > 2.0 x ULN • AST > 2.0 x ULN b. Renal: • Persistently positive (2 out of 3 consecutive tests ≥ 1+) for protein on urine dipstick. In the event of a positive test eligibility may be confirmed by a quantitative total urine protein measurement of < 500 mg/24 hrs • Persistently positive (2 out of 3 consecutive tests ≥ trace positive) for blood on urine dipstick. In the event of a positive test eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field • Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault < 50 mL/min (MDRD or CKD-EPI formulas can be used instead of Cockcroft-Gault for estimation of GFR in patients with low body weight after discussion with Sponsor Medical Monitor) c. Cardiac Troponin I > ULN at Screening* d. LDL-C > 130 mg/dL at Screening* e. Any other laboratory abnormalities which, in the opinion of the Investigator or the Sponsor, would make the patient unsuitable for inclusion 6. Uncontrolled hypertension (BP > 160/100 mm Hg) 7. History of thrombocytopenia (platelet count < 100,000/mm^3) or bleeding diathesis or coagulopathy or clinically-significant abnormality in coagulation parameters at Screening* 8. History of heart failure with NYHA greater than Class II 9. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1 10. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B 11. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated 12. Treatment with another investigational drug, biological agent, or device within 1-month of screening*, or 5 half-lives of investigational agent, whichever is longer 13. Unwilling to comply with lifestyle requirements (Section 6.3)

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	Exclusion Criteria *Continued* 14. Use of any of the following: a. Statins, omega-3 fatty acids (prescription and OTC), or fibrates unless on a stable dose for at least 3 months prior to screening* and dose and regimen expected to remain constant during the treatment period. Patients taking OTC omega-3 fatty acids should make every effort to remain on the same brand throughout the study b. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to screening* c. Systemic corticosteroids or anabolic steroids within 6 weeks prior to screening* unless approved by the Sponsor Medical Monitor d. Atypical antipsychotic medications (e.g., olanzapine and clozapine) unless on a stable dose for at least 3 months prior to screening* and dose and regimen expected to remain stable throughout the study e. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to screening* and dose and regimen expected to remain constant during the treatment period f. Glybera gene therapy within 2 years prior to screening* g. Oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, and apixaban) unless on a stable dose for at least 4 weeks prior to screening* and regular clinical monitoring is performed h. Tamoxifen, estrogens or progestins unless on a stable dose for at least 4 months prior to screening* and dose and regimen expected to remain constant during the treatment period i. Plasma apheresis within 4 weeks prior to screening* or planned during the study j. Prior exposure to ISIS 304801 k. Any other medication unless stable at least 4 weeks prior to screening* (Occasional or intermittent use of over-the-counter medications will be allowed at Investigator's discretion) 15. Blood donation of 50 to 499 mL within 30 days of screening* or of > 499 mL within 60 days of screening* 16. Known hypersensitivity to any of the excipients of the Study Drug (ISIS 304801 or placebo) 17. Have any other conditions, including new or worsening of existing condition, which, in the opinion of the Investigator or the Sponsor would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the study *(Group 3) or Qualification (Groups 1 and 2)
Treatment Group	Volanesorsen 300 mg once per week
Study Drug Administration	Volanesorsen will be administered as subcutaneous (SC) injections.
Dose Adjustments	Dose adjustments, including dose interruptions and/or decreasing the dose frequency will be allowed for safety or tolerability after consultation with the Sponsor Medical Monitor.

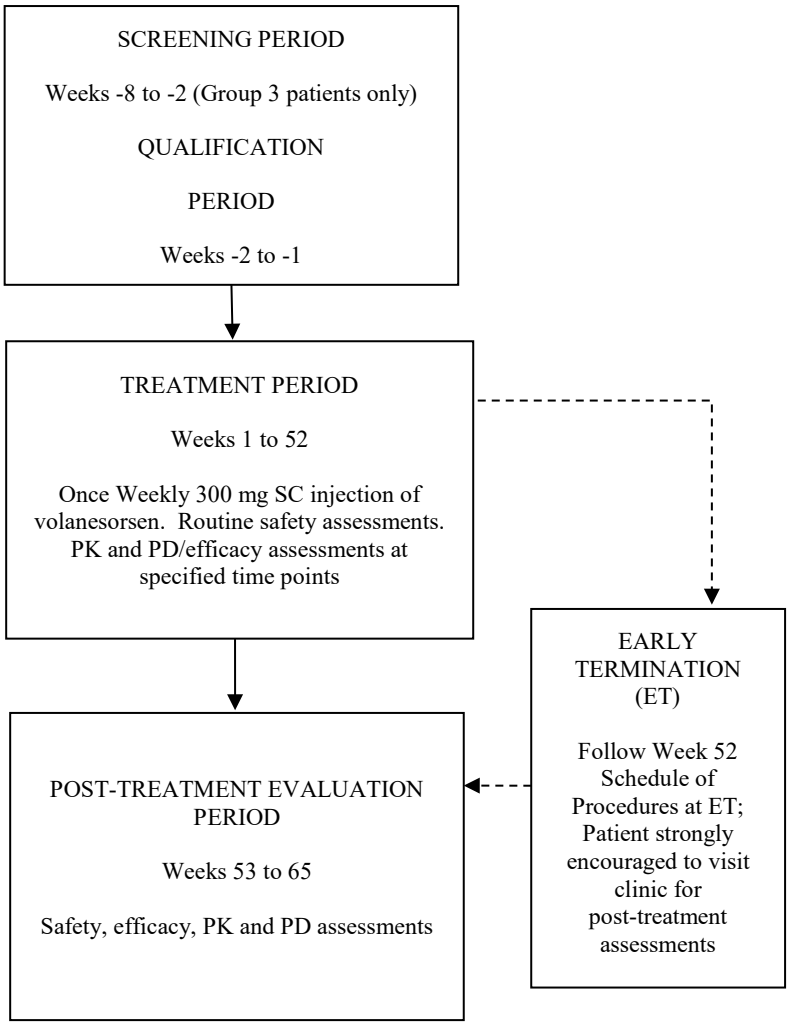
PROTOCOL SYNOPSIS *Continued*

Rationale for Dose and Schedule Selection	The dose of 300 mg once weekly was chosen for the double-blinded placebo-controlled Phase 3 index studies (ISIS 304801-CS6 and ISIS 304801-CS16) based on the pharmacodynamic and safety analysis of the Phase 2 studies (Section 2.4) which included a subset of patients with FCS. The same dose of 300 mg once weekly will be used in this open-label study of FCS patients.
Study Visit Schedule and Procedures	The study for an individual patient will generally consist of the following periods: • Group 1 and 2 patients (participated in ISIS 304801-CS6 or ISIS 304801-CS16 index study): A qualification period of up to 2 weeks (unless approved by the Sponsor). Please refer to Section 4.1 and Appendix A • Group 3 patients (did not participate in an index study): An up to 8-week screening and qualification period, including a diet stabilization period of at least 6 weeks (screening and diet stabilization period may be reduced, per Sponsor approval, if the patient is following a diet for optimal control of TGs and disease management prior to screening). Please refer to Section 6.1.2 and Appendix A • All patients: o A 52-week treatment period during which volanesorsen will be administered as a once weekly SC injection o A 13-week post-treatment evaluation period The patients, Investigators, study staff, and the Sponsor will remain blinded to lipid data through the last patient's Week 13 visit of the open-label study or until results from the database locks for the ISIS 304801-CS6 and ISIS 304801-CS16 index studies becomes available, whichever comes first. Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), adverse events (AE), concomitant medication/procedure information, lipid panel, volanesorsen plasma concentrations, immunogenicity (IM) testing, liver/spleen magnetic resonance imaging (MRI), ECGs, echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Dietary counseling will be repeated at intervals throughout the treatment and follow-up period and a daily food/drink diary will be completed for the week prior to each quarterly visit by each patient. Following the Week 52 visit, patients will enter the 13-week post-treatment evaluation period.

PROTOCOL SYNOPSIS *Continued*

Safety and Tolerability Evaluations	Overall safety and tolerability of volanesorsen will be assessed by determining the incidence and severity of adverse and serious adverse events (including independently adjudicated events of acute pancreatitis and MACE), withdrawals due to adverse events, and changes in laboratory and other safety parameters.
Planned Analyses	Safety Endpoints: • Adverse events including adjudicated events of acute pancreatitis and MACE • Vital signs and weight • Physical examinations • Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis) • Echocardiography • Electrocardiograms (ECGs) • Use of concomitant medications • MRIs Efficacy Endpoints: • Percent change and absolute change from baseline in fasting TG • Frequency and severity of patient reported abdominal pain during the treatment period • Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-high-density lipoprotein-cholesterol (non-HDL-C), apolipoprotein B [apoB], high-density lipoprotein-cholesterol (HDL-C), apolipoprotein A-1 [apoA-1], very-low-density lipoprotein-cholesterol (VLDL-C), and LDL-C • Percent change from baseline in fasting total apolipoprotein C-III (apoC-III) • Quality of Life questionnaires (EQ-5D, SF-36) • Adjudicated acute pancreatitis event rate • Other symptoms: eruptive xanthoma, lipemia retinalis
Pharmacokinetic Evaluations	Plasma samples will be taken from all patients for the measurement of volanesorsen as follows: trough levels (pre-dose) throughout treatment and post-treatment levels during the post-treatment follow-up period. In a subset of patients, more frequent assessment of plasma concentrations of volanesorsen will be performed to determine volanesorsen pharmacokinetic parameters. Plasma sample collection time points are detailed in Appendix A and Appendix C.
Statistical Considerations	No sample size calculations were performed as this is an open-label study.
Sponsor	Ionis Pharmaceuticals, Inc.
Collaborator	Akcea Therapeutics

STUDY DESIGN AND TREATMENT SCHEMA



STUDY GLOSSARY

Abbreviation/Acronym	Definition
ADA	anti-drug antibody
AE	adverse Event
ALP	alkaline Phosphatase
ALT	alanine Aminotransferase
ANA	antinuclear Antibody
apoA-1	apolipoprotein A-1
apoB	apolipoprotein B
apoC-III	apolipoprotein C-III
apoE	apolipoprotein E
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
CBC	complete blood count
C_{max}	maximum observed drug concentration
CRF	case report form
DNA	deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
ET	early termination
FAS	full analysis set
FCS	Familial Chylomicronemia Syndrome
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
GPIHBP1	Glycosylphosphatidylinositol-anchored HDL-binding Protein 1
HAPI	Heritability and Phenotype Intervention
HbA1c	Glycated Hemoglobin
HDL	High-Density Lipoprotein
HDL-C	High-Density Lipoprotein-Cholesterol
hsCRP	High-sensitivity C-reactive protein
ICH	International Conference on Harmonization
IDL	Intermediate density lipoprotein
IEC	Independent Ethics Committee
IM	immunogenicity
Index Studies	ISIS 304801-CS6 and ISIS 304801-CS16

STUDY GLOSSARY *Continued*

INR	International Normalized Ratio
IRB	Institutional Review Board
IXRS	Interactive Voice/Web-Response System
LDL	Low-Density Lipoprotein
LDL-C	Low-Density Lipoprotein-Cholesterol
LMF1	Lipase Maturation Factor 1
LPL	Lipoprotein Lipase
MACE	Major Acute Cardiovascular Event
MOE	2′-*O*-(2-methoxyethyl)
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NCS	not clinically-significant
NOAEL	No-Observed-Adverse-Effect Level
non-HDL-C	Non-High-Density Lipoprotein-Cholesterol
OTC	over the counter
PFS	prefilled syringe
PD	pharmacodynamic
PK	pharmacokinetic
PPS	per protocol set
PT	prothrombin time
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SUSAR	suspected unexpected serious adverse reaction
T2DM	type 2 diabetes mellitus
T_{max}	time to maximal concentration
TG	triglycerides
Treatment-emergent	occurring after first dose of Study Drug
TRL	Triglyceride-Rich Lipoproteins
ULN	upper limit of normal
VLDL	Very-Low-Density Lipoprotein
VLDL-C	Very-Low-Density Lipoprotein-Cholesterol
VLDL-TG	Lipoprotein-Triglyceride
WMA	World Medical Association

1. OBJECTIVES

The objective of the study is to evaluate the safety and efficacy of dosing and extended dosing with volanesorsen in patients with familial chylomicronemia syndrome.

2. BACKGROUND AND RATIONALE

2.1 Overview of Disease

Familial Chylomicronemia Syndrome (FCS) is an inherited disease characterized by severe hypertriglyceridemia and chylomicronemia, and risk or history of pancreatitis. It is a rare autosomal recessive disease that can be diagnosed either in childhood or adulthood.

Fasting plasma triglyceride (TG) levels in FCS patients are typically 10-fold to 100-fold above normal (1,500 to 15,000 mg/dL), despite extreme dietary fat restriction (20 g or approximately 15-20% of daily calorie intake) (Brunzell 1999-2011). Patients with FCS often present in infancy or childhood with frequent and severe abdominal pain, repetitive colicky pain, repeated episodes of potentially fatal acute pancreatitis, and failure to thrive (Brunzell 1999-2011; Tremblay et al. 2011). Physical examination frequently reveals eruptive xanthomas, lipemia retinalis and hepatosplenomegaly, and plasma from patients appears lactescent, interfering with determination of other laboratory parameters (Tremblay et al. 2011).

Patients with fasting triglyceride levels > 10 mmol/L probably have a component of chylomicronemia. Clinical diagnosis would include evidence of clinical features of chylomicronemia syndrome and secondary causes such as uncontrolled type 1 or type 2 diabetes mellitus (T2DM), hypothyroidism, poor diet, alcohol use, nephrotic syndrome or use of associated medications should be ruled out. The diagnosis of FCS may be made more specifically by genotyping or confirmation of very low or absent lipoprotein lipase (LPL) enzyme activity in post heparin plasma (Brunzell 1999-2011).

Patients with FCS carry a heavy burden of medical complications, the most serious, as described above, being an extreme risk of recurrent and potentially fatal pancreatitis. Due to the recurrent episodes of acute pancreatitis, these patients may also develop chronic pancreatitis and signs of exocrine or endocrine pancreatic insufficiency, including diabetes mellitus (Gaudet et al. 2013). While the pathophysiology underlying chylomicron-related pancreatitis has not been completely elucidated, 1 hypothesis is that large chylomicrons lodged in pancreatic capillaries are exposed to pancreatic lipase, with the subsequent release of free fatty acids through the hydrolysis of chylomicron-associated TGs. High concentrations of free fatty acids are thought to damage pancreatic cells leading to emergent pancreatitis (Yang et al. 2009; Berglund et al. 2012).

The etiology of extreme hypertriglyceridemia in FCS is considered to be ineffective triglyceride clearance, due to an extremely low level of LPL activity. LPL normally functions to hydrolyze triglycerides (TG) in chylomicrons along the luminal surface of capillaries, mainly in heart, skeletal muscle, and adipose tissue, promoting triglyceride clearance from the circulation. LPL is regulated by a number of key genes, and loss-of-function mutations in one of these genes, or the LPL gene itself, results in FCS (Surendran et al. 2012). In addition to loss of function mutations, null mutations, and nonsense mutations in the LPL gene, other genes currently identified in FCS patients, and known to directly influence LPL activity include: apolipoprotein C-II (APOC2) a cofactor for LPL (Schuster et al. 2011); apolipoprotein A-V

(APOA5) an enhancer of LPL activity (Schaap et al. 2004); lipase maturation Factor 1 (LMF1), a transmembrane protein involved in LPL maturation (Doolittle et al. 2009); glycosylphosphatidylinositol-anchored HDL-binding protein 1 (GPIHBP1), a capillary endothelial cell protein that provides a platform for LPL-mediated processing of chylomicrons (Beigneux et al. 2007).

2.2 Therapeutic Rationale

Apolipoprotein C-III (ApoC-III), a key regulator of plasma triglyceride levels, is a 79 amino acid glycoprotein synthesized principally in the liver (Ooi et al. 2008; Figure 1). ApoC-III is a major regulator of lipoprotein metabolism and plays a pivotal role in regulating plasma TG levels (Chan et al. 2008). It is a component of triglyceride-rich lipoproteins (TRLs) and a potent inhibitor of LPL (Lemieux et al. 2003). At higher concentrations apoC-III also inhibits hepatic lipase activity (Kinnunen and Ehnolm 1976), an enzyme which plays an important role in the conversion of dense very-low-density lipoprotein (VLDL) to intermediate density lipoprotein (IDL) and to LDL (Mendivil et al. 2010), as well as in the remodeling of HDL (Brown et al. 2010). In addition, increased apoC-III content adversely affects apoE-mediated hepatic uptake of TG-rich remnants (Mann et al. 1997). Thus, elevated plasma apoC-III levels are associated with impaired hydrolysis and retarded clearance of TG-rich particles, resulting in the accumulation of lipoprotein-triglyceride (VLDL-TG) and chylomicrons in plasma and the development of hypertriglyceridemia (Ito et al. 1990).

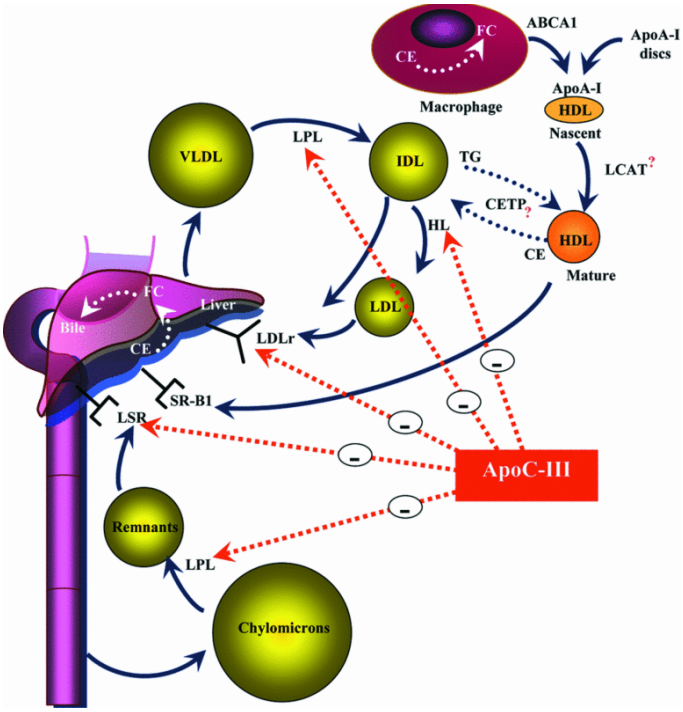


Figure 1 ApoC-III Regulates Lipoprotein Metabolism by Multiple Mechanisms

From Ooi et al. 2008; ABCA1 = ATP-binding cassette A1, apo = apolipoprotein, CE = cholesterol ester, CETP = cholesterol ester transfer protein, FC = free cholesterol, HDL = high-density lipoprotein, HL = hepatic lipase, IDL = intermediate-density lipoprotein, LCAT = lecithin cholesterol acyltransferase, LDL = low-density lipoprotein, LDLr = LDL receptor, LPL = lipoprotein lipase, LSR = lipolysis-stimulated receptor, SR-B1 = scavenger receptor B-1, TG = triglyceride, VLDL = very low-density lipoprotein.

Mechanistically, FCS is primarily a consequence of ineffective clearance of TRL. ApoC-III is a prominent component of TRL (e.g., VLDL and chylomicrons). In addition to its role in inhibiting LPL, apoC-III inhibits TRL remnant (TG-depleted remnant lipoprotein) uptake by hepatic lipoprotein receptors by steric inhibition of the interaction of apoE with these receptors.

Human genetic data have demonstrated positive phenotypic associations with loss (e.g., null or nonsense mutations) and negative effects with gain of function mutations (Atzmon et al. 2006; Pollin et al. 2008; Petersen et al. 2010). A novel nonsense mutation in the apoC-III gene was identified in the heritability and phenotype intervention (HAPI) heart study in Old Order Amish that results in lower plasma apoC-III and TG levels and lower LDL-C, increased HDL-C and reduced atherosclerosis (Pollin et al. 2008). In another study involving a group of 214 Ashkenazi Jews of advanced age (had passed or nearly reached 100 years of age), genotype analysis revealed a polymorphism in the apoC-III gene (APOC3-641CC genotype) with a clear pattern of age-dependent frequency that was associated with significantly lower levels of apoC-III protein, a favorable lipoprotein profile and increased longevity (Atzmon et al. 2006). In contrast to the Amish and Ashkenazi apoC-III polymorphisms associated with lower plasma TG, apoC-III polymorphisms associated with higher plasma TG have also been recently described (Petersen et al. 2010). In a cohort of lean (mean body mass index [BMI] = 24.7 ± 3.6 kg/m^2) Asian Indians, carriers of apoC-III variant alleles (C-482T, T-455C, or both) were noted to have significantly higher plasma apoC-III and TG levels, and decreased ability to clear postprandial plasma TG from the circulation. Taken together, the available data strongly support the development of a therapy that reduces plasma apoC-III levels in order to reduce the very high circulating triglyceride and chylomicron levels that are accompanied by increasing risk for acute pancreatitis.

Given the profound reductions in TGs observed with volanesorsen treatment in FCS patients who have no detectable LPL activity (See Section 2.3.4), and the mechanistic data available to date on apoC-III function, potential mechanisms that explain how apoC-III inhibition results in triglyceride reduction in FCS patients include: (1) enhancing the very small residual amounts of LPL activity that these patients may have, below the limit of detection of the assay in many cases (2) potentially enhanced activity of other lipases also involved in the metabolism and breakdown of TGs, such as hepatic lipase or endothelial lipase (Kinnunen and Ehnolm 1976), and (3) apoC-III interaction with Apolipoprotein E (apoE), an important factor in liver reuptake of lipid particles by blocking apoE-mediated uptake of lipid particles in the liver (Breyer et al. 1999), and therefore, reducing apoC-III might enhance apoE-mediated uptake of lipid particles. Volanesorsen-mediated reduction of apoC-III could be contributing to one or all of these mechanisms resulting in the observed potent and sustained reductions in TG.

Through a novel apoC-III lowering mechanism of action, volanesorsen may provide the potential to manage triglyceride levels in FCS patients.

2.3 Volanesorsen

2.3.1 Mechanism of Action

Volanesorsen is a second-generation antisense oligonucleotide (ASO) drug targeted to human apoC-III. It is complementary to a region within the 3′ untranslated region of the apoC-III messenger ribonucleic acid (mRNA) and binds to the mRNA by Watson and Crick base pairing.

The hybridization (binding) of volanesorsen to the cognate mRNA, results in the RNase H1-mediated degradation of the apoC-III mRNA, thus preventing production of the apoC-III protein. Maximal antisense-mediated reduction of target mRNA levels is typically greater than 90% of control levels in sensitive tissues (Crooke and Bennett 1996; Zhang et al. 2010). Furthermore, reduction in target mRNA levels using this approach correlates directly with a subsequent reduction in target protein levels.

2.3.2 Chemistry

Chemically, volanesorsen is a synthetic oligomer of 20 nucleotides (i.e., a 20-mer) that are connected sequentially by phosphorothioate linkages. The nucleotide sequence of volanesorsen (Figure 2) is complementary to a 20-nucleotide stretch within the 3′ untranslated region of the apoC-III mRNA transcript at base position 489-508. Structurally, the oligonucleotide has 3 regions. Two (2) of them, the 5 nucleotides at the 5′ end and the 5 nucleotides at the 3′ end, are composed of 2′-*O*-(2-methoxyethyl) (MOE)-modified ribonucleotides. These MOE-modified nucleotides confer (1) increased affinity to the target mRNA (Altmann et al. 1996; McKay et al. 1999), (2) increased resistance to exonucleases and endonucleases (thereby increasing stability in tissue) (Geary et al. 2003), and (3) amelioration of some of the high dose toxicities thereby resulting in an improved safety profile compared to first generation antisense drugs containing phosphorothioate modified oligodeoxynucleotides (DNA) (Henry et al. 2000). The third region, the central portion of the oligonucleotide, is composed of 10 oligodeoxynucleotides. This chimeric design is called a MOE-Gapmer, and volanesorsen employs this chimeric structure to enable use of the RNase H1-mechanism for antisense activity. This is because while the 2′-MOE modification confers increased stability and affinity, it does not support RNase H1 catalysis of RNA hybridized to 2′-MOE-modified nucleotides (McKay et al. 1999). This is caused by conformational changes induced in the heteroduplex by 2′-alkoxy:RNA hybrids that are not recognized by RNase H1 enzymes (Inoue et al. 1987; Monia et al. 1993). By limiting the 2′-MOE modification to nucleotides flanking the phosphorothioate oligodeoxynucleotide core, the beneficial attributes of the 2′-MOE chemistry are preserved while also retaining RNase H1 recognition.

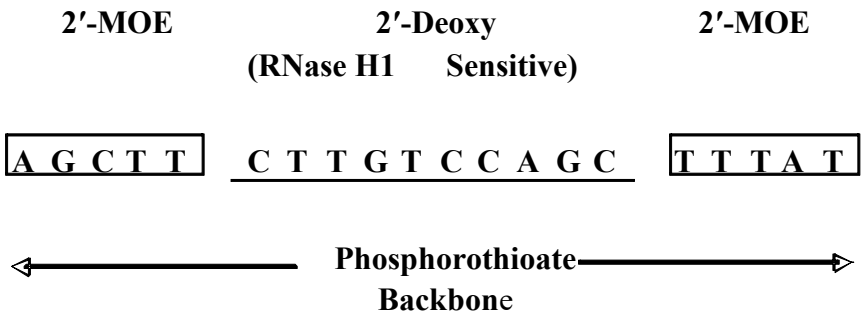


Figure 2 Design of Chimeric 2′-MOE Phosphorothioate Oligonucleotides (MOE-Gapmer). The sequence of volanesorsen is shown

2.3.3 Preclinical Experience

Inhibition of apoC-III using volanesorsen has been shown to potently reduce hepatic apoC-III mRNA as well as plasma apoC-III protein and TG in a dose- and time-dependent fashion in several species, including human apoC-III transgenic mice, and other rodent and monkey models. Treatment with volanesorsen also resulted in reduced VLDL and chylomicron TG and reduced postprandial TG in hypertriglyceridemic monkeys (Graham et al. 2013).

The pharmacokinetics (PK) and toxicity of volanesorsen have been assessed in mice, rats, and cynomolgus monkeys. General toxicity studies with volanesorsen for up to 39 weeks of treatment followed by up to a 20-week recovery period are complete. The preclinical toxicology program for volanesorsen consists of single dose safety pharmacology studies in the monkey (cardiovascular) and mouse (neurobehavioral and pulmonary assessment studies), *in vitro* and *in vivo* genetic toxicity assessment, repeat dose fertility and/or developmental reproductive toxicology studies in the mouse and rabbit and evaluation in the *in vitro* human Ether-á-go-go-related gene (hERG) assay.

Volanesorsen treatment-related findings in mice and monkeys were generally consistent with those expected for the 2′-MOE-class of ASOs. Treatment-related findings included effects consistent with drug accumulation in tissues in rodents and monkeys, species-dependent proinflammatory response in rodents and monkeys and complement activation and reductions in platelet counts in the monkey. In the mouse and monkey general toxicity studies, reduction of hepatic apoC-III mRNA (> 75%) was not associated with any findings that could be considered related to the pharmacologic inhibition of apoC-III for up to 39 weeks of treatment.

The long-term, chronic toxicology studies in rodents with volanesorsen produced a significant proinflammatory response that led to subsequent effects on the heart at high doses. The rodent species are most sensitive to the proinflammatory effects of antisense molecules. Importantly, these effects on the heart were not observed in the monkey chronic toxicity studies even at the highest doses tested where drug exposure was higher than that in rodents.

Because these changes were not observed in monkeys, the findings in the heart are considered to be rodent-specific and not relevant to humans. Nevertheless, such effects will be monitored by measurement of echocardiograms that will be included in this clinical study.

Volanesorsen caused no untoward effects in safety pharmacology studies (*in vitro* and *in vivo*) and was non-genotoxic (*in vitro* and *in vivo*). Volanesorsen had no effects on fertility or embryo/fetal development in the mouse or rabbit reproductive toxicity studies. In these studies, volanesorsen was detected in placental tissue but not in fetal tissue indicating that little, if any, drug was able to cross the placenta to reach the fetus. Reduction of apoC-III mRNA (64% in males and 47% in females) also did not affect fertility or cause untoward effects on embryo/fetal development in mice.

Detailed information concerning the preclinical studies conducted with volanesorsen can be found in the volanesorsen Investigator's Brochure.

2.3.4 Clinical Experience

Detailed information concerning the clinical studies conducted with volanesorsen can be found in the volanesorsen Investigator's Brochure. A summary is included below.

Volanesorsen has been evaluated in one Phase 1 study and two Phase 2 studies, all double blinded and placebo controlled. The total exposures comprise 99 patients and healthy volunteers administered volanesorsen from 50 to 400 mg subcutaneously up to 3 months (compared to 37 administered placebo).

All clinical trials of volanesorsen have shown large and clinically meaningful reductions in fasting plasma apoC-III and TG (~80% and 70%, respectively, mean reduction from baseline with 300 mg dose) with a very high degree of consistency of response between the different patient groups. This includes healthy volunteers, patients with moderate to severe hypertriglyceridemia not on background TG-lowering therapy, patients with moderate to severe hypertriglyceridemia on a background stable fibrate therapy (Gaudet et al. 2015), patients with FCS, and patients with T2DM.

In a Phase 2 study, 3 patients with FCS were treated with 300 mg/wk volanesorsen in an open-label fashion. These patients had a mean baseline fasting TG level of 1,844 mg/dL and all 3 patients achieved TG levels below or close to 500 mg/dL during the dosing period out to Day 92 (Figure 3). Two (2) of the FCS patients had an absolute reduction in fasting TG in excess of 1,500 mg/dL (Gaudet et al. 2014).

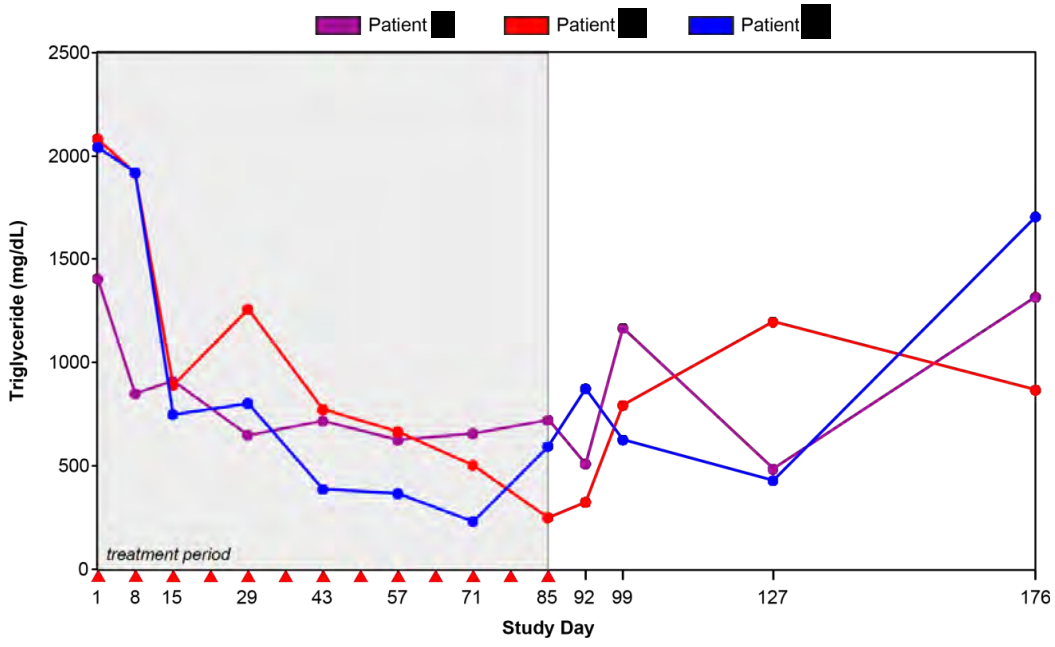


Figure 3 Fasting Triglycerides in Patients with FCS Treated with Volanesorsen

In clinical studies conducted to date volanesorsen has been well-tolerated and has shown a favorable safety profile. There has been no clinical or laboratory evidence of drug-drug interactions.

In the completed studies there have been no volanesorsen associated laboratory abnormalities suggestive of an effect on the renal (serum creatinine, proteinuria) or hepatic systems (alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin). In Phase 2 studies, there was a mild decrease of platelet count associated with volanesorsen administration that recovered in the post-treatment period and was not associated with platelet-related adverse events (AEs). In the blinded ongoing clinical trials of ISIS 304801, 2 patients of 142 dosed (as of February 29, 2016) had a decrease in platelet count to less than 50,000/mm^3 in the absence of major bleeding or clinically-relevant non-major bleeding and had Study Drug paused as per the monitoring and stopping rules for platelet counts (Section 8.6.3). Platelet counts recovered following suspension of dosing.

The most frequently observed AEs with volanesorsen were local reactions at the injection site. Local cutaneous reactions at the injection site defined as those events presenting as either pain, tenderness, erythema, pruritus or swelling occurring on the day of injection and persisting for at least 2 days were infrequent (~15% of injections), were almost always mild, resolved spontaneously, were non-progressive, and were not associated with systemic sequelae.

2.4 Rationale for Dose and Schedule of Administration

The dose and schedule selected for this study is 300 mg per week for 52 weeks. The dose of 300 mg per week is supported by both the cumulative nonclinical data available to date and the Phase 2 clinical data. In nonclinical studies, volanesorsen treatment-related effects in rodents and monkeys were consistent with drug accumulation in tissues and also include species-specific proinflammatory responses. In the monkey, the No-Observed-Adverse-Effect Level (NOAEL) was defined by the cumulative clinical pathology results and histopathology data which provide an adequate clinical margin. No nonclinical findings were considered to be related to the pharmacologic inhibition of apoC-III.

The safety data to date suggest that volanesorsen has been well-tolerated at dose levels up to 300 mg in patients with high triglycerides (including type 2 diabetes patients and administration in combination with fibrates and statins) with the most common AEs being local to the injection site and predominantly mild. A pooled analysis of safety for the Phase 2 studies did not demonstrate any clear difference in safety or tolerability between the different doses tested (100 mg, 200 mg, and 300 mg per week for 13 weeks).

Analysis of the cohorts in which volanesorsen was studied at different doses demonstrates dose-dependent pharmacology with respect to pharmacodynamic (PD) effect on the target, apoC-III, with a clear difference in the TG-lowering effect between the different doses in the 100 mg to 300 mg dose range as compared to placebo.

In addition to the nonclinical and clinical experience of volanesorsen, the dose and schedule of administration is supported by the preclinical and clinical safety experience of several other 2′-MOE-modified ASOs that have been safely administered intravenously and subcutaneously in multiple clinical studies at doses up to 1000 mg and for treatment durations that exceed 24 months (Santos et al. 2015).

3. EXPERIMENTAL PLAN

3.1 Study Design

This is an open-label study of:

Group 1: ISIS 304801-CS6 (index study) roll over FCS patients

Group 2: ISIS 304801-CS16 (index study) roll over FCS patients

Group 3: FCS patients who did not participate in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies

Up to approximately 70 patients will receive 300 mg once weekly volanesorsen for 52 weeks.

Following the Week 52 visit, patients enter a 13-week post-treatment evaluation period.

3.2 Number of Study Centers

This study will be conducted at multiple centers worldwide.

3.3 Number of Patients

Up to approximately 70 patients will be dosed.

3.4 Overall Study Duration and Follow-up

The Study will consist of the following periods:

3.4.1 Group 1 and 2 Patients (participated in ISIS 304801-CS6 or ISIS 304801–CS16 index study): Qualification

A period of up to 2 weeks (unless approved by the Sponsor) is given to complete qualification assessments outlined in the Schedule of Procedures. Please refer to Section 4.1 and Appendix A.

3.4.2 Group 3 Patients (did not participate in an index study): Screening/Qualification

An up to 8-week screening and qualification period, including a diet stabilization period of at least 6 weeks (screening and diet stabilization period may be reduced, per Sponsor approval, if the patient is following a diet for optimal control of TGs and disease management prior to screening. Please refer to Section 6.1.2 and Appendix A.

3.4.3 Treatment

The treatment period is 52 weeks. Eligible patients will report to the Study Center for assessments at specified intervals throughout the 52-week treatment period as detailed in the Schedule of Procedures (Appendix A). During the treatment period, volanesorsen is administered by SC injection once weekly.

3.4.4 Post-Treatment

The post-treatment evaluation period is 13 weeks and consists of 2 Study Center visits on Weeks 58 and 65.

3.5 End-of-Study

The End-of-Study is last patient, last visit.

3.6 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will review (as needed) safety, tolerability and efficacy data collected on volanesorsen during this study. Based on its ongoing assessment of the safety and tolerability of volanesorsen, the DSMB will provide recommendations to the Sponsor for modifying, stopping or continuing the study as planned. Details on the safety assessments, frequency of review and meeting schedules are outlined in the DSMB Charter and/or the statistical analysis plan (SAP).

4. PATIENT ENROLLMENT

4.1 Screening/Qualification

Before patients may be enrolled into the study, the Sponsor requires a copy of the Study Center's written independent ethics committee/institutional review board (IEC/IRB) approval of the protocol, informed consent form, and all other patient information.

Patients or their legally acceptable representatives must sign the consent form before any study-specific procedures or evaluations related to this open-label study are performed.

Groups 1 and 2 (Qualification): During the qualification period, the eligibility of the patient to enroll in the open-label study will be determined. Final assessments from the ISIS 304801-CS6 or ISIS 304801-CS16 studies may be used for qualification. A period of up to 2 weeks after completion of the ISIS 304801-CS6 or ISIS 304801-CS16 index studies (unless approved by the Sponsor) is given to complete qualification. Qualified patients will retain the unique patient identification number that was assigned to them during the ISIS 304801-CS6 or ISIS 304801-CS16 index studies. The patient identification number will be used to identify the patient throughout the extension trial and must be used on all study documentation related to that patient. The patient identification number must remain constant throughout the extension trial.

Group 3 (Screening and Qualification): At the time of consent, the patient will be considered enrolled into the study and will be assigned a unique screening number before any study procedures, including screening procedures, are performed. At the time of enrollment, patients will be assigned a unique patient identification number. This number will be used to identify the patient throughout the trial and must be used on all study documentation related to that patient. The screening number and patient identification number must remain constant throughout the entire trial. In the event the patient is re-consented and re-screened the patient must be given a new screening number. Screening numbers and patient identification numbers, once assigned, will not be re-used.

4.2 Enrollment

Patients will be enrolled into the treatment phase of the study after all Screening (Group3) and qualification assessments have been completed and after the Investigator has verified that they are eligible per criteria in Sections 5.1 and 5.2. No patient may begin treatment prior to enrollment.

Eligible patients will be enrolled using an Interactive Voice/Web-Response System (IXRS).

5. PATIENT ELIGIBILITY

To be eligible to participate in this study candidates must meet the following eligibility criteria within 2 weeks of Study Day 1, or at the time point specified in the individual eligibility criterion listed.

5.1 Inclusion Criteria

1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law

2. Age ≥ 18 years at time of informed consent

3. Groups 1 and 2: Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement.

   Groups 2 and 3: Patients must also meet the following criteria in order to enter into the open-label Study:

   a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L)

   b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) by documentation of the following:

      - Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1)

   c. Group 2: Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 index study
      Group 3: Fasting TG ≥ 750 mg/dL at Screening for this open-label study

4. Able and willing to participate in a 65-week study

5. Satisfy 1 of the following:

   a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved), abstinent*, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration.

   b. Males: Surgically sterile, abstinent* or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer

to Section 6.3.1) from the time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration.

* Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception

5.2 Exclusion Criteria

1. Diabetes mellitus with any of the following:
   a. Newly diagnosed within 12 weeks of screening*
   b. HbA1c ≥ 9.0% at Screening*
   c. Recent change in anti-diabetic pharmacotherapy (change in dosage or addition of new medication within 12 weeks of screening* [with the exception of ± 10 units of insulin])
   d. Anticipated need to change dose or type of medication during the treatment period of the Study (with the exception of ± 10 units of insulin)
   e. Current use of GLP-1 agonists
2. Severe hypertriglyceridemia other than due to familial chylomicronemia syndrome
3. Active pancreatitis within 4 weeks prior to screening*
4. History within 6 months of screening* of acute or unstable cardiac ischemia (myocardial infarction, acute coronary syndrome, new onset angina), stroke, transient ischemic attack or unstable congestive cardiac failure requiring a change in medication or major surgery within 3 months of screening*
5. Any of the following laboratory values at Screening*
   a. Hepatic:
      - Total bilirubin > upper limit of normal (ULN), unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL
      - ALT > 2.0 x ULN
      - AST > 2.0 x ULN
   b. Renal:
      - Persistently positive (2 out of 3 consecutive tests ≥ 1+) for protein on urine dipstick. In the event of a positive test eligibility may be confirmed by a quantitative total urine protein measurement of < 500 mg/24 hrs

- Persistently positive (2 out of 3 consecutive tests ≥ trace positive) for blood on urine dipstick. In the event of a positive test eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field
- Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault < 50 mL/min (MDRD or CKD-EPI formulas can be used instead of Cockcroft-Gault for estimation of GFR in patients with low body weight after discussion with Sponsor Medical Monitor)

c. Cardiac Troponin I > ULN at Screening*

d. LDL-C > 130 mg/dL at Screening*

e. Any other laboratory abnormalities which, in the opinion of the Investigator or the Sponsor, would make the patient unsuitable for inclusion

6. Uncontrolled hypertension (BP > 160/100 mm Hg)
7. History of thrombocytopenia (platelet count < 100,000/mm^3) or bleeding diathesis or coagulopathy or clinically-significant abnormality in coagulation parameters at Screening*
8. History of heart failure with NYHA greater than Class II
9. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1
10. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B
11. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated
12. Treatment with another investigational drug, biological agent, or device within 1-month of screening*, or 5 half-lives of investigational agent, whichever is longer
13. Unwilling to comply with lifestyle requirements (Section 6.3)
14. Use of any of the following:

    a. Statins, omega-3 fatty acids (prescription and OTC), or fibrates unless on a stable dose for at least 3 months prior to screening* and dose and regimen expected to remain constant during the treatment period. Patients taking OTC omega-3 fatty acids should make every effort to remain on the same brand throughout the study

    b. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to screening*

    c. Systemic corticosteroids or anabolic steroids within 6 weeks prior to screening* unless approved by the Sponsor Medical Monitor

d. Atypical antipsychotic medications (e.g., olanzapine and clozapine) unless on a stable dose for at least 3 months prior to screening* and dose and regimen expected to remain stable throughout the study

e. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to screening* and dose and regimen expected to remain constant during the treatment period

f. Glybera gene therapy within 2 years prior to screening*

g. Oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, and apixaban) unless on a stable dose for at least 4 weeks prior to screening* and regular clinical monitoring is performed

h. Tamoxifen, estrogens or progestins unless on a stable dose for at least 4 months prior to screening* and dose and regimen expected to remain constant during the treatment period

i. Plasma apheresis within 4 weeks prior to screening* or planned during the study

j. Prior exposure to ISIS 304801

k. Any other medication unless stable at least 4 weeks prior to screening* (Occasional or intermittent use of over-the-counter medications will be allowed at Investigator's discretion)

15. Blood donation of 50 to 499 mL within 30 days of screening* or of > 499 mL within 60 days of screening*

16. Known hypersensitivity to any of the excipients of the Study Drug (ISIS 304801 or placebo)

17. Have any other conditions, including new or worsening of existing condition, which, in the opinion of the Investigator or the Sponsor would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the study

*(Group 3) or Qualification (Groups 1 and 2)

6. STUDY PROCEDURES

6.1 Study Schedule

All required study procedures are outlined in Appendices A, B, C, and D.

6.1.1 Qualification (Groups 1 and 2)

Please refer to Section 4.1 and Appendix A.

6.1.2 Screening and Qualification (Group 3)

Before any study-specific procedures or evaluations are initiated, patients must sign and date the informed consent form. An 8-week period, including a diet stabilization period of at least

6 weeks (screening and diet stabilization period may be reduced, per Sponsor approval, if the patient is following a diet for optimal control of TGs and disease management prior to screening) is given to perform the screening evaluations. The qualification assessments will be performed at Week -2 to -1, ideally after patient eligibility has been determined, and on Study Day 1. Abnormal screening results may be retested for review by the Study Medical Monitor for eligibility purposes

6.1.3 Treatment Period

The patients, Investigators, study staff, and the Sponsor will remain blinded to lipid data through the last patient's Week 13 visit of the open-label study or until results from the database locks for the ISIS 304801-CS6 and ISIS 304801-CS16 index studies become available, whichever comes first.

During the treatment period, patients will report to the study center for clinic visits a minimum of 5 times during Weeks 1-52 (see Schedule of Procedures in Appendix A). Study Drug will be administered once weekly (Section 8.1). Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), AEs, concomitant medication/procedure information, lipid panel, volanesorsen plasma concentrations, immunogenicity (IM) testing, liver/spleen MRI, ECGs, echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Adverse events at the injection site should be collected as adverse events. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period and all patients will complete a daily food diary for one week prior to their quarterly visit. All blood and urine samples should be collected prior to volanesorsen administration. Blood sampling at Weeks 2.5, 4, 6, 8, 10, 12, 15, 17, 19, 21, 23, 25, 28, 30, 32, 34, 36, 40, 42, 44, 46, 48, and 50 may be conducted by a home healthcare nurse. Approval for study procedures to be conducted by a home healthcare nurse on other outpatient visit days will require prior approval by the Sponsor. Patients must be fasted prior to drawing all blood samples and samples drawn locally should also be sent to the central laboratory for analysis whenever possible. Every effort should be made to ensure the previous week's dose is given 7 days prior to a scheduled clinic visit. Dosing instructions and training will be provided to the patient where applicable.

All reasonable attempts should be made to ensure compliance with the visit schedule as outlined in Appendix A. However, in the event that a visit does not occur or is delayed, all subsequent visits should be calculated based on the time elapsed since Day 1 rather than from the date of the previous visit.

6.1.4 Pharmacokinetic (PK) Subgroup

A subgroup of patients will participate in an extended PK collection. Patients in this subgroup will have more frequent PK sampling over a 24-hour period following the first dose on Study Day 1 in order to evaluate the plasma PK parameters of volanesorsen. Patients in this subgroup will have an additional visit to the clinic, or by a home healthcare nurse, on Day 2 to collect a 24-hour post-dose blood draw after dosing on Day 1. The detailed PK sampling schedules are outlined in Appendix C.

Participation in the PK subgroup is optional for sites and patients, and consent may be withdrawn for the subgroup-specific procedures (e.g., multiple blood draws for PK) without being

withdrawn from the study. If a patient withdraws consent from the subgroup procedures, he/she should remain on study and continue to follow all the non-subgroup assessments and procedures as outlined in Appendix A.

6.1.5 Post-Treatment Period

After completion of the Week 52 visit assessments, patients will enter the 13-week post-treatment evaluation period. This period consists of 4 Study Center visits on Weeks 54, 56, and 58 (which may be conducted by a home healthcare nurse), and Week 65 as outlined in the Schedule of Procedures in Appendix A.

6.2 Additional Study Assessments

6.2.1 Laboratory Assessments

Laboratory analyte samples will be collected throughout the study. A list of these analytes is contained in Appendix B.

Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1-week and determined not to have met a stopping rule before dosing can continue.

If there is no reportable platelet count within 14 days of the last platelet count, the Investigator will contact the patient to hold dosing until a new platelet count is obtained and reviewed.

All platelet count results will be promptly reviewed by the Investigator to ensure that the count has not met the stopping rule and to determine whether the rate of decline is suggestive that the patient could be approaching the dose pause rule of 75,000/mm^3.

Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor.

6.2.2 Physical Exams and Vital Signs

Physical exams and vital signs will be performed as indicated in the Schedule of Procedures (Appendix A). Vital signs should include weight, blood pressure, pulse rate, respiratory rate and body temperature. Blood pressure and pulse rate will be recorded after the patient has been in a sitting position for at least 5 minutes. Semi-supine systolic and diastolic blood pressure should always be measured on the same arm (preferentially on the left arm). Height will be measured at the Day 1 visit.

6.2.2.1 Eruptive Xanthoma

At each visit, patients will be asked whether they have had any episodes of eruptive xanthoma since their last visit and the number/duration of the events will be recorded. Physical exams should also include skin examination for presence/resolution of eruptive xanthomas. If a patient experiences an episode of eruptive xanthoma during the study, photos of the area should be taken, if possible.

6.2.2.2 Lipemia Retinalis

If possible, lipemia retinalis will be assessed by fundus photography prior to administration of the first dose of Study Drug (for ISIS 304801-CS16 rollover patients) and repeated at Week 52. Images will be evaluated by an independent assessor, blinded to the patient's treatment assignment.

6.2.3 Echocardiography

Echocardiography for assessment of left and right ventricular function and mitral and aortic valve function will be conducted at Week 26 and Week 52 in all patients. For the purpose of assessment of treatment-emergent changes, all echocardiograms will be evaluated on an ongoing basis by an independent central reader. Results will be provided to the DSMB for their review.

6.2.4 ECG

The ECG will be recorded after the patient has been resting in a supine position for at least 5 minutes. ECGs will be performed in triplicate at Week 13, Week 26, Week 38, Week 52, and Week 65.

6.2.5 MRI

MRI of the liver and spleen will be conducted at Week 52 for all patients for whom MRI is not contraindicated, e.g., patients having metal implants.

MRIs will be conducted using standardized procedures and settings. MRIs will be read by an independent central reader to assess liver fat and liver and spleen size**.**

6.2.6 Quality of Life Assessments

All patients will complete Quality of Life Questionnaires (EQ-5D and SF-36) at Week 1, Week 13, Week 26, Week 52, and Week 65.

6.2.7 Disease Symptom Diary

All patients will complete a symptom questionnaire once a week starting at the beginning of the qualification period and continuing to the end of the post-treatment follow-up period.

6.2.8 Diet Monitoring

The diets of patients enrolled in the study will be monitored as follows:

1. All patients will be required to maintain a 7-day food diary prior to Week 1, Week 13, Week 26, Week 52, and Week 65.

2. Patients will receive diet/alcohol counseling by qualified study personnel at clinic visits throughout the course of the study. Qualified study personnel will telephone the patient to provide diet/alcohol counseling for visits that are conducted by a clinical service.

3. In addition to the 7-day food diary and the diet /alcohol counseling during clinic visits, telephone calls from a dietitian or qualified study personnel to assess as to how each patient is maintaining their diet will be conducted randomly during the treatment and post treatment follow-up periods.

6.2.9 Family History

Family history of hypertriglyceridemia and pancreatitis will be collected for each patient.

6.3 Restriction on the Lifestyle of Patients

6.3.1 Contraception Requirements

All male patients and women of childbearing potential must refrain from sperm/egg donation and either be abstinent* or, if engaged in sexual relations of child-bearing potential, practice effective contraception from the time of signing the informed consent form until at least 13 weeks after their last dose of study treatment.

Male patients must also encourage their female partner to use effective contraception from the time of signing the informed consent until 13 weeks after the subject's last dose of study treatment.

For the purposes of this Study, women of childbearing potential are defined as any female who has experienced menarche, and who does not meet 1 of the following conditions:

- Postmenopausal: 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved
- 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Post hysterectomy

For the purposes of the study, effective contraception is defined as follows:

For male patients:

- Effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the use of condoms together with spermicidal foam/gel/film/ cream/suppository. Male patients must also encourage their female partner to use effective contraception from the time of signing the informed consent until 3 months after the patient's last dose of study treatment. Effective contraceptive for the female partner includes: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or barrier methods (female condom*, diaphragm, sponge, cervical cap) together with spermicidal foam/gel/film/cream/suppository. Male patients with partners that are pregnant must use condoms to ensure that the fetus is not exposed to the Study Drug.

For female patients:

- Using 1 or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or any 2 barrier methods (a combination of male or female condom* with diaphragm, sponge, or cervical cap) together with spermicidal foam/gel/film/cream/suppository.

*Note: A female condom and a male condom should not be used together as friction between the two can result in either product failing.

* Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception

6.3.2 Other Requirements

All patients will be required to fast for at least 10 hours and preferably not more than 12 hours before visits requiring fasted blood sampling.

All patients will be encouraged to follow a diet comprising ≤ 20 g fat per day during the study.

Alcohol should not be consumed during the study.

All patients will be given an instruction card that must be presented to the treating physician if a suspected case of pancreatitis occurs. The card will explain that the patient is in a clinical trial and that serum lipase and/or amylase measures should be done in order to adjudicate the event, based on Atlanta Classification (Banks et al. 2013). If serum or amylase activity is less than 3 x upper limit of normal (ULN), imaging, preferably contrast-enhanced computed tomography, should be considered to confirm the diagnosis of acute pancreatitis per the Atlanta Criteria.

7. STUDY DRUG

7.1 Volanesorsen Description

Volanesorsen drug product (ISIS 304801) characteristics are listed in Table 1.

Volanesorsen (ISIS 304801) is contained in glass prefilled syringes (PFS). Volanesorsen and its storage and preparation instructions will be provided by the Sponsor or designee. Volanesorsen must be stored securely at 2° to 8° C and be protected from light.

Table 1 Volanesorsen (ISIS 304801) Characteristics

Strength	200 mg/mL
Volume/Formulation	1.5 mL solution per PFS
Dose	300 mg once weekly
Route of Administration	SC

7.2 Packaging and Labeling

The Sponsor will provide the Investigator with packaged volanesorsen labeled (ISIS 304801) in accordance with specific country regulatory requirements.

7.3 Study Drug Accountability

The study staff is required to document the receipt, dispensing, and return/destruction of volanesorsen provided by the Sponsor. The Study Center must return all unused volanesorsen to the Sponsor or designee. All used syringes must be disposed of as per the site's hazardous waste destruction policy.

8. TREATMENT OF PATIENTS

8.1 Volanesorsen Administration

For each individual patient, volanesorsen will be administered subcutaneously as a single 1.5 mL 300 mg injection once weekly for Weeks 1-52. Patients entering this ISIS 304801-CS7 study on a reduced dose or dose frequency of Study Drug (volanesorsen), for safety or tolerability reasons in their index study (ISIS 304801-CS6 or ISIS 304801-CS16), will receive a reduced dose or dose frequency of volanesorsen for continued safety or tolerability as outlined in Sections 8.5 and 8.6. Patients entering this CS7 study having dose or dose frequency reduced in the CS16 index study after 13 weeks of treatment, as outlined in CS16 Amendment 4 Section 8.7, can receive the 300 mg once weekly dose of volanesorsen.

Patients should receive 1 dose per week, with weeks always defined relative to Study Day 1. For example if a patient receives the first dose on a Monday, subsequent doses should be given on Mondays, if possible. If a patient misses an injection, or if dosing on the usual day is not possible, the patient can reschedule the injection provided that 2 doses are administered at least 2 days apart.

Every effort should be made to ensure the previous week's dose is given 7 days prior to a scheduled clinic visit.

Please refer to the Study Drug Manual provided by the Sponsor for more detailed instructions for volanesorsen preparation and administration.

8.2 Other Protocol-Required Drugs

There are no other protocol-required drugs (Section 6.2.5).

8.3 Other Protocol-Required Treatment Procedures

There are no other protocol required treatment procedures for this study.

8.4 Treatment Precautions

There are no specific treatment precautions required for this study.

8.5 Safety Monitoring Rules

Please refer also to the 'Guidance for Investigator' section of the Investigator's Brochure.

For the purposes of safety monitoring baseline is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 (e.g., qualification assessments or assessments from the final visits of ISIS 304801-CS6 and ISIS 304801-CS16 index studies if used for qualification).

In addition to the standard monitoring of clinical safety parameters, the following guidelines are provided for the monitoring of selected parameters chosen based on preclinical and clinical observations.

Confirmation Guidance: At any time during the study (Treatment or Post-Treatment Periods), the initial clinical laboratory results meeting the safety monitoring or stopping criteria presented below **must be confirmed** by performing measurements (ideally in the same laboratory that performed the initial measurement) on new specimens. All new specimen collections should take place as soon as possible (ideally within 3 days of the initial collection). For stopping rules, if the initial laboratory result is observed during the Treatment Period, the results from the retest **must be available** prior to administering the next dose of volanesorsen.

In addition to the safety monitoring parameters listed below, the Sponsor may request confirmation of additional lab values.

Re-dosing Guidance: Patients with initial laboratory test values that reach a stopping rule must not be re-dosed until the re-test results are available. In general, patients who do not meet the stopping rules based upon retest may continue dosing. However, the Investigator and the Sponsor Medical Monitor (or appropriately qualified designee) should confer as to whether additional close monitoring of the patient is appropriate. Reduction in dose or dose frequency may also be initiated as noted in Section 8.7. If any of the stopping criteria described below (refer to Sections 8.6.1 to 8.6.3) are met, the patient will be dose paused or permanently discontinued (as described in the stopping criterion concerned) from further treatment with volanesorsen, and evaluated fully as outlined below and in consultation with the Sponsor Medical Monitor or appropriately qualified designee, and will be followed up in accordance with Section 8.8 of the protocol.

8.5.1 Safety Monitoring for Liver Chemistry Tests

The following rules are adapted from the draft guidance for industry, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," issued by the U.S. Department of Health and Human Services, Food and Drug Administration, July 2009. For a definition of Baseline please refer to guidance in Section 8.5 above.

In the event of an ALT or AST measurement that is > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) at any time during the study (Treatment or Post-Treatment Period), the initial measurement(s) should be confirmed as described above. Additional confirmatory measurements should also be performed if ALT or AST levels increase to 5 x ULN.

Frequency of Repeat Measurements: Patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) should have their liver chemistry tests (ALT, AST, alkaline phosphatase (ALP), international normalized ratio (INR) and total bilirubin) retested at least once-weekly until ALT and AST levels become ≤ 1.2 x ULN or 1.2 x baseline value if the baseline value was > ULN.

Further Investigation into Liver Chemistry Elevations: For patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), the following evaluations should be performed:

1. Obtain a more detailed history of symptoms and prior and concurrent diseases
2. Obtain further history for concomitant drug use (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
3. Obtain a history for exposure to environmental chemical agents and travel
4. Serology for viral hepatitis (HAV IgM, HBsAg, HCV antibody, CMV IgM, and EBV antibody panel)
5. Serology for autoimmune hepatitis (e.g., antinuclear antibody [ANA])

Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic CT or MRI scans, may be performed at the discretion of the Investigator, in consultation with the Sponsor Medical Monitor. Repetition of the above evaluations should be considered if a patient's ALT and/or AST levels reach 5 x ULN.

8.5.2 Safety Monitoring for Platelet Count Results

Actions to be taken in the event of reduced platelet count are shown in Table 2 in Section 8.6.3.

Additional lab tests will be determined by the Sponsor Medical Monitor or designee in consultation with the Investigator.

Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor (See also Stopping Rules Section 8.6.3).

8.5.3 Safety Monitoring for Minor Bleeding Events

Minor bleeding events are those that do not fulfill the criteria for major bleeding or clinically-relevant, non-major bleeding events (which are defined in Section 8.6.3), for example excess bruising, petechiae, gingival bleeding on brushing teeth. If a minor bleeding event occurs, the Investigator must notify the Sponsor Medical Monitor and additional testing of coagulation parameters activated partial thromboplastin time (aPTT), prothrombin time (PT), INR and platelet count should be performed.

8.5.4 Safety Monitoring for Constitutional Symptoms

Patients will be instructed to promptly report any signs of symptoms of fever or constitutional symptoms that may arise during the study and the Investigator should closely evaluate all potential causes, including concomitant illness. Patients that experience persistent constitutional symptoms should be discussed with the Sponsor Medical Monitor or designee to determine whether additional monitoring or laboratory tests are required.

8.5.5 Safety Monitoring for LDL-C Elevations

Beginning at Week 13, laboratory alerts will be in place to notify the Investigator if a patient has a low-density lipoprotein-cholesterol (LDL-C) > 160 mg/dL (> 130 mg/dL for patients with T2DM) on 2 consecutive visits. If this occurs, LDL-C values for this patient will be unblinded for the remainder of the study and the Investigator will be encouraged to initiate/adjust treatment

to lower LDL-C according to country-specific guidelines (e.g., initiate statin therapy or increase the statin dose for patients who are already on treatment).

8.5.6 Safety Monitoring for Insulin, Oral Antidiabetic Medication and Glucose

All patients on insulin will monitor their glucose levels with a glucometer as per standard practice guidelines and bring their glucometer or glucometer log printout to every clinic visit. In addition, patients who are not on insulin but use a glucometer should also bring their glucometer and/or glucometer log printout to every clinic visit.

- The Investigator or delegate will review the glucometer reading or printout at every clinic visit to evaluate if fasting pre-breakfast self-monitored plasma glucose values exceed threshold values as per the Safety Monitoring Rules for Hyperglycemia below.

All diabetic patients will note any changes in their insulin dose and /or oral antidiabetic therapy, as well as any hypoglycemic episode they may experience.

- The Investigator or delegate will ask patients at every clinic visit if they made changes in their insulin dose or oral antidiabetic therapy, and if they experienced a hypoglycemic episode.
    - Patients will be instructed on the monitoring and management of hypoglycemic episodes at each visit.
    - Documented symptomatic hypoglycemic episodes should be captured as adverse events in the adverse event CRF. Documented symptomatic hypoglycemia is defined as typical hypoglycemia symptoms accompanied by measured plasma glucose ≤ 70 mg/dL (≤ 3.9 mmol/L).
    - Any changes in insulin dose or oral antidiabetic therapy should be captured into the Concomitant Medication CRF.

8.5.7 Safety Monitoring for Documented Severe Hypoglycemia

A **documented severe hypoglycemic event** is defined as 1 in which the patient requires assistance of another person to obtain treatment for the event and has a plasma glucose level ≤ 70 mg/dL (≤ 3.9 mmol/L). The rescue treatment of hypoglycemia may include IV glucose or buccal or intramuscular glucagon.

The definition of severe symptomatic hypoglycemia includes all episodes in which neurological impairment was severe enough to prevent self-treatment and which were thus thought to place patients at risk for injury to themselves or others. Note that "requires assistance" means that the patient could not help himself or herself. Someone being kind that assists spontaneously the patient when not necessary does not qualify as "requires assistance."

Severe hypoglycemia will be qualified as a SAE only if it fulfills SAE criteria.

If a patient presents with symptoms of hypoglycemia, the Investigator will need to take immediate action to confirm the patient's glucose level and treat the patient accordingly.

The experience of hypoglycemia may vary greatly from patient to patient. However, there are certain classical signs and symptoms, of which patients should be aware as a clue that their blood glucose may be low. Common symptoms include headache, heart pounding, confusion, disorientation, numbness or tingling, pale skin, shakiness or tremulousness, increased appetite, anxiousness or nervousness, lightheadedness or dizziness, sweating, and weakness. Coma could occur if blood sugar correction is not performed.

If patients suspect they might be having a hypoglycemia reaction, they should check their blood glucose using their meters as soon as possible, before treatment if possible, provided they feel it is safe to do so. If there is doubt about safety they should treat the event first, using some sugar, milk, or juice for example, then obtain and record a blood glucose value as soon as possible thereafter. The time and nature of treatment should be noted, and especially if any blood glucose result was before or after treatment. It would be helpful for the patient to note if a contributory factor (e.g., missed or reduced meals, unaccustomed physical activity) occurred earlier in the day of the event.

8.5.8 Safety Monitoring for Hyperglycemia

Upward dose titration and/or addition of any other anti-hyperglycemic agent(s) will not be allowed during the course of the study, unless specific threshold values are met at Week 13 or later and confirmed on subsequent testing (ideally within 1-week of the initial test).

HbA1c is monitored every 3 months throughout the study. In addition, patients on insulin should self-monitor their plasma glucose (SMPG) routinely on a glucometer as per practice guidelines. If a fasting pre-breakfast SMPG value exceeds the specific glycemic limit, the patient should check it again on the following 2 days. If all the fasting pre-breakfast values on 3 consecutive days exceed the specific limit, the patient should contact the Investigator and an unscheduled central laboratory FPG measurement and HbA1c should be performed.

The threshold values are defined as:

- FPG > 270 mg/dL (15.0 mmol/L)
- HbA1c > 9% (for patients with baseline HbA1c < 8% and HbA1c increase of more than 1% from baseline (for patients with baseline HbA1c ≥ 8 and < 9%)

In case of confirmed FPG/HbA1c above the threshold value, the Investigator should ensure that no reasonable explanation exists for insufficient glucose control and in particular that:

- Plasma glucose was actually measured in the fasting condition (i.e., after at least 10 hours fast)
- Absence of intercurrent disease which may jeopardize glycemic control. In case of an emergency (e.g., surgery, infection), the Investigator can take appropriate measures for glycemic control
- Compliance to treatment is appropriate
- Compliance to diet and lifestyle is appropriate

If any of the above can reasonably explain the insufficient glycemic control, the Investigator should consider the following:

- Investigation and treatment of intercurrent disease (to be reported in adverse event (AE)/concomitant medication parts of the e-CRF)
- Stress on the absolute need to be compliant to treatment
- Organize a specific interview with a Registered Dietician or other qualified nutrition professional and stress on the absolute need to be compliant to diet and lifestyle recommendations

A FPG/HbA1c follow-up assessment should be arranged after appropriate action has been taken. If none from the above-mentioned reasons can be found, or if appropriate action fails to decrease FPG/HbA1c under the threshold values, additional medication may be introduced at the Investigator's discretion and according to local guidelines after discussion with the Sponsor Medical Monitor.

8.5.9 Acute Pancreatitis

If a patient has an episode of acute pancreatitis, dosing with Study Drug should be suspended temporarily until the patient is clinically stable. The suitability of the patient for continued dosing and the need for any modification to treatment schedule (refer to Section 8.7) will be determined by the Investigator in consultation with the Study Medical Monitor.

8.6 Stopping Rules

For the purposes of stopping rules baseline is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1.

8.6.1 Stopping Rules for Liver Chemistry Elevations

In the event of laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor,** dosing of a patient with volanesorsen will be stopped permanently; values that are not confirmed due to failure to retest or missing lab values will be presumed confirmed:

1. ALT or AST > 8 x ULN, which is confirmed
2. ALT or AST > 5 x ULN, which is confirmed and persists for ≥ 2 weeks
3. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed **and** total bilirubin > 2 x ULN or INR > 1.5
4. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed, and the new appearance (i.e., onset coincides with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> ULN) felt by the Investigator to be potentially related to hepatic inflammation

8.6.2 Stopping Rules for Renal Function Test Results

In the event of a persistent elevation that is observed over 2 consecutive weeks, for any of the 3 criteria below, dosing of a patient with volanesorsen may be stopped temporarily:

1. Serum creatinine increase that fulfill all of the following criteria: ≥ 0.3 mg/dL (26.5 µmol/L) and ≥ 40% above baseline creatinine values and > ULN

2. Proteinuria, dipstick 2 + (confirmed by dipstick retest and then further confirmed by a quantitative total urine protein measurement of > 1.0 g/24-hour)

3. Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault ≤ 40 mL/min that is confirmed by a 24-hour urine collection

The possible dosing re-initiation or follow-up schedule for any events meeting either of these criteria will be determined by the Investigator **in consultation with** the Sponsor Medical Monitor or designee.

8.6.3 Stopping Rules for Platelet Count Results

Actions to be taken in the event of a low platelet count are summarized in Table 2 below.

In the event of a platelet count less than 75,000/mm^3 that is associated with major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with volanesorsen will be stopped permanently. The follow-up schedule for any events meeting this stopping criterion will be determined by the Investigator in consultation with the Sponsor Medical Monitor.

In the event of any platelet count less than 50,000/mm^3, or a rate of decline ≥ 50% between two consecutive assessments, irrespective of the platelet level, then dosing of a patient with volanesorsen will be stopped permanently. Platelet count will be monitored daily until 2 successive values show improvement then monitored every 2-3 days until platelet count is stable.

Administration of steroids is recommended for patients whose platelet count is less than 25,000/mm^3. Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (**note:** may require continuation with oral steroids after methylprednisolone).

In the event of a platelet count less than 75,000/mm^3, and in the absence of major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with volanesorsen should be suspended temporarily until the platelet count has recovered to> 100,000/mm^3. If dosing is continued it should be at a reduced dose frequency of 300 mg every 2 weeks or a reduced dose of 150 mg per week (refer to Section 8.7). The suitability of the patient for continued dosing will be determined by the Investigator in consultation with the Study Medical Monitor and will be based on factors such as the original rate of decline in the patient's platelet count, whether any bleeding events were experienced by the patient, and the speed of recovery of platelet count upon holding of dosing.

If after the first dosing rechallenge the platelet count again falls below 75,000/mm^3, then dosing of the patient with Study Drug will be stopped permanently.

Following a rechallenge platelet count should be tested every week until count is stable.

Any unreportable platelet count result must be rechecked and determined not to have met a stopping rule before dosing can continue.

If there is no reportable platelet count within 14 days of the last platelet count, the Investigator will contact the patient to hold dosing until a new platelet count is obtained and reviewed.

Definition of Major Bleeding Events (Schulman et al. 2005):

- Fatal bleeding, and/or
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarterial or pericardial, or intramuscular with compartment syndrome, and/or
- Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more within 24 hours, or leading to transfusion of 2 or more units of whole or red cells

Definition of Clinically-Relevant, Non-Major Bleeding Events (Schulman et al. 2005):

1. Multiple-source bleeding
2. Spontaneous hematoma > 25 cm^2
3. Excessive wound hematoma (not injection site related)
4. Macroscopic hematuria (spontaneous or lasting > 24 hours if associated with an intervention)
5. Spontaneous rectal bleeding; epitasis, gingival bleeding, hemoptysis, hematemesis
6. Bleeding after venipuncture for > 5 minutes

Table 2 Actions in Patients with Low Platelet Count

Platelet Count on Rx	Drug Dose	Monitoring
Normal range, > 140K/mm^3	No action	Monitor every 2 weeks
100K-140K/mm^3	No action	Closer observation Monitor every 1-week until stable*
75K-100K/mm^3	Permanently reduce dose frequency to 300 mg every 2 weeks or reduce dose to 150 mg weekly	Closer observation Monitor every 1-week
50K-75K/mm^3	If occurs while on dose of 300 mg every 2 weeks or 150 mg every week then permanently discontinue Study Drug, otherwise dose pause. When platelet count returns to > 100K/mm^3 restart dosing at dose frequency of 300 mg every 2 weeks or 150 mg weekly **only if approved by Sponsor Medical Monitor**	Closer observation Monitor every 2-3 days until 2 successive values show improvement Consider discontinuation of antiplatelet agents/NSAIDS/ anticoagulant medication
25K-50K/mm^3 or a rate of decline ≥ 50% between two consecutive assessments, irrespective of the platelet level	Permanently discontinue Study Drug	Closer observation Monitor daily until 2 successive values show improvement then monitor every 2-3 days until platelet count stable Discontinue antiplatelet agents/NSAIDS/anticoagulant medication while platelet count < 50K/mm^3 if possible
< 25K/mm^3	Permanently discontinue Study Drug	Closer observation: Monitor daily until 2 successive values show improvement then monitor every 2-3 days until platelet count stable Steroids recommended** Consider need for hospitalization and referral to hematologist Discontinue antiplatelet agents/NSAIDS/anticoagulant medication while platelet count < 50K/mm^3 if possible

* At least 3 consecutive values measured weekly that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3

** Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (**note**: may require continuation with oral steroids after methyl prednisolone)

8.7 Adjustment of Dose Frequency

Dose adjustments for platelet count reduction must be made in accordance with Section 8.6.3 and Table 2 (above).

Other dose adjustments, including dose interruptions, and/or decreasing the dose or dose frequency will be allowed for safety and tolerability. Any proposed adjustment to treatment

schedule must be discussed with, and approved by, the Study Medical Monitor prior to initiation. Up to 2 adjustments in the treatment schedule may be allowed.

Patients may be dose paused in response to AEs after consultation with Study Medical Monitor.

8.8 Discontinuation of Study Treatment

A patient must permanently discontinue study treatment for any of the following:

- The patient becomes pregnant. Report the pregnancy according to instructions in Section 9.5.4
- The patient withdraws consent
- The patient experiences an AE that necessitates permanent discontinuation of study treatment
- The patient develops laboratory test abnormalities that meet any of the stopping rules listed in Section 8.6

The reason for discontinuation of study treatment must be recorded in the CRF and source documentation.

8.8.1 Follow-up Visits for Early Termination from Treatment Period

Any patient who discontinues early from the Treatment Period should be followed as per the platelet monitoring rules shown in Table 2 in Section 8.6.3 for the first 6 weeks after discontinuing Study Drug. Following this period, if the platelet count is stable (at least 3 consecutive values that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3), the next platelet count should be taken within at least 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug. Patients should also be strongly encouraged to attend applicable landmark visits at Weeks 12, 13, 25, 26, and 50, 52 (calculated based on the time elapsed since Day 1) to collect fasting lipid panels and conduct safety assessments in accordance with the Schedule of Procedures in Appendix A. Any patient who discontinues treatment after Week 44 should also be strongly encouraged to attend a final follow-up visit (Week 65 visit assessments) approximately 13 weeks after their last dose of Study Drug, in addition to the applicable landmark visits.

If the patient declines or is unable to participate in the above, an early termination (ET) visit (Week 52 visit assessments) should be performed at the time of withdrawal, at a minimum, and ideally within 2 weeks from the last dose of Study Drug.

8.8.2 Follow-up Visits for Early Termination from Post-Treatment Follow-up Period

The patient who requests to withdraw from the study during the Post-Treatment Follow-up Period should be encouraged to follow the platelet monitoring rules shown in Table 2 in Section 8.6.3 for the first 6 weeks after discontinuing Study Drug. Following this period, if the platelet count is stable (at least 3 consecutive values that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3), the next platelet count should be taken within at least 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug.

Patients should also be encouraged to undergo a final follow-up visit (Week 65, see Appendix A) prior to leaving the study.

If a patient withdraws due to an AE at any time during the study, the Investigator should arrange for the patient to have appropriate follow-up until the AE has resolved or stabilized.

8.9 Withdrawal of Patients from the Study

Patients must be withdrawn from the study for any of the following:

- Withdrawal of consent
- The patient is unwilling or unable to comply with the protocol

Other reasons for withdrawal of patients from the study might include:

- At the discretion of the Investigator for medical reasons
- At the discretion of the Investigator or Sponsor for noncompliance
- Significant protocol deviation

All efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information, including the reason for withdrawal from study, must be recorded in the CRF.

Any patient who withdraws consent to participate in the study will be removed from further treatment and study observation immediately upon the date of request. These patients should be encouraged to complete the ET study procedures and observations at the time of withdrawal (see Section 8.8 and Appendix A).

For patients withdrawn for reasons other than withdrawal of consent every effort should be made to complete the early termination study procedures and observations at the time of withdrawal (see Section 8.8 and Appendix A).

8.10 Concomitant Therapy and Procedures

The use of concomitant therapies or procedures defined below must be recorded on the patient's CRF. AEs related to administration of these therapies or procedures must also be documented on the appropriate CRF.

8.10.1 Concomitant Therapy

A concomitant therapy is any non-protocol specified drug or substance (including over-the-counter medications, herbal medications and vitamin supplements) administered between signing informed consent and completion of the post-treatment follow-up period. All concomitant medications/treatments and significant non-drug therapies (including supplements and assistive devices) received by a patient, including changes in the patient's current medications, must be recorded in the patient's source documents and CRF. Patients taking over the counter (OTC) omega-3 fatty acids should make every effort to remain on the same brand throughout the study.

Allowed Concomitant Therapy

Any medications deemed necessary by the Investigator are allowed except those listed in the disallowed concomitant therapy.

Disallowed Concomitant Therapy

No lipid lowering therapies (e.g., fibrates, niacin, fish oil or other products containing omega-3 fatty acids [including OTC preparations]), -glucagon-like peptide-1 (GLP-1) agonists, Glybera, or systemic corticosteroids may be started or adjusted after baseline qualification. Doses of existing oral anti-diabetic medication, oral contraceptives, hormone replacement therapy, anticoagulants, or drugs or dietary supplements with potential lipid-altering effects should not be adjusted. Study patients are prohibited from receiving other experimental agents during the study. This includes marketed agents at experimental dosages that are being tested for the treatment of hypertriglyceridemia.

Patients should consult with the Site Investigator or designee prior to initiating any new medication, including non-prescription or herbal compounds or any other non-drug therapy.

8.10.2 Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between signing of informed consent and Week 65 visit.

Disallowed Concomitant Procedure

Plasma apheresis is not allowed during the study.

8.11 Treatment Compliance

Compliance with treatment dosing is to be monitored and recorded by Study Center staff. The Study Center staff is required to document the receipt, dispensing, and return/destruction of volanesorsen. Patients that are self-administering volanesorsen at home must record treatment in a dosing diary that will be reviewed periodically by Study Center staff and the Clinical Monitor.

9. SERIOUS AND NON-SERIOUS ADVERSE EVENT REPORTING

9.1 Sponsor Review of Safety Information

Safety information will be collected, reviewed, and evaluated by the Sponsor in accordance with the Safety Management Plan throughout the conduct of the clinical trial.

9.2 Regulatory Requirements

The Sponsor is responsible for regulatory submissions and reporting to the Investigators of serious adverse events (SAEs) including suspected unexpected serious adverse reactions (SUSARs) per the International Conference on Harmonization (ICH) guidelines E2A and ICH E6. Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines.

Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) will be notified of any SAE according to applicable regulations. The Independent DSMB will be notified of any SAE as specified in the DSMB charter.

In addition to the Investigator's assessment of relatedness, the Sponsor or designee will evaluate the available information and perform an independent assessment of relatedness. While the Sponsor may upgrade an Investigator's decision it is not permissible to downgrade the Investigator's opinion for the purposes of determining whether the SAE meets the definition of a SUSAR.

The following table identifies the SAEs that the Sponsor or designee will not report on an individual basis in an expedited manner because they are anticipated to occur in the study population independent of volanesorsen exposure. The Investigator still has the responsibility to report all SAEs to the Sponsor as described in Sections 9.4.1 to 9.4.3.5.

Table 3 Expected Event for the Protocol Defined Population by Preferred Term and the Expected Incidence

Preferred Term	Expected Incidence in the Protocol Defined Population (Gaudet et al. 2010 and 2013)
Pancreatitis associated events including the PTs of hereditary pancreatitis, pancreatitis, pancreatitis acute, pancreatitis chronic, pancreatitis necrotizing, pancreatitis relapsing	0.2-0.35 events per patient-year

Fatal pancreatitis associated events will be considered as unexpected and are reportable. The Sponsor and DSMB will monitor non-fatal pancreatitis associated SAEs using the incidence rate of the event compared to the rate expected in a non-volanesorsen exposed population. If the aggregate analysis indicates that an event is occurring significantly more frequently or at a greater severity than expected, then the event will be reported.

SAEs not specified in the table will be evaluated on case by case basis to determine whether there is a reasonable possibility that the drug caused the event. If the event is considered by the Sponsor or designee to meet the definition of a SUSAR the event will be reported.

9.3 Definitions

9.3.1 Adverse Event

An adverse event is any unfavorable and unintended sign (including a clinically-significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the study or use of investigational drug product, whether or not the AE is considered related to the investigational drug product.

9.3.2 Adverse Reaction and Suspected Adverse Reaction

An adverse reaction is any adverse event caused by volanesorsen.

A suspected adverse reaction is any adverse event for which there is a reasonable possibility that volanesorsen drug caused the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

9.3.3 Serious Adverse Event (SAE)

A serious adverse event is any adverse event that in the view of either the Investigator or Sponsor, meets any of the following criteria:

- Results in death
- Is life threatening: that is, poses an immediate risk of death at the time of the event

An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Hospitalization is defined as an admission of greater than 24 hours to a medical facility and does not always qualify as an AE
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly or birth defect in the offspring of the patient (whether the patient is male or female)
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

9.4 Monitoring and Recording Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the study (i.e., before informed consent) should be recorded as Medical History and not recorded as AEs unless the pre-existing condition worsened. The Investigator should always group signs and symptoms into a single term that constitutes a **single unifying diagnosis** if possible.

9.4.1 Serious Adverse Events

In the interest of patient safety, and in order to fulfill regulatory requirements**,** all SAEs (regardless of their relationship to volanesorsen) should be reported to the Sponsor or designee within 24 hours of the Study Center's first knowledge of the event. The collection of SAEs will begin after the patient signs the informed consent form and stop at the end of the patient's

follow-up period which is defined as the Week 65 visit. When the Investigator is reporting by telephone, it is important to speak to someone in person versus leaving a message. An Initial Serious Adverse Event Form should be completed and a copy should be faxed to the Sponsor or designee.

Detailed information should be actively sought and included on Follow-Up Serious Adverse Event Forms as soon as additional information becomes available. All SAEs will be followed until resolution. SAEs that remain ongoing past the patient's last protocol-specified follow-up visit will be evaluated by the Investigator and Sponsor. If the Investigator and Sponsor agree the patient's condition is unlikely to resolve, the Investigator and Sponsor will determine the follow-up requirement.

9.4.2 Non-Serious Adverse Events

The recording of non-serious AEs will begin after the patient signs the informed consent form and will stop at the end of the patient's follow-up period, which is defined as the Week 65 visit. The Investigator will monitor each patient closely and record all observed or volunteered AEs on the Adverse Event Case Report Form.

9.4.3 Evaluation of Adverse Events (Serious and Non-Serious)

The Investigator's opinion of the following should be documented on the Adverse Event Case Report Form:

9.4.3.1 Relationship to the Study Drug

The event's relationship to volanesorsen is characterized by 1 of the following:

- **Related:** There is clear evidence that the event is related to the use of volanesorsen, e.g., confirmation by positive rechallenge test
- **Possible:** The event cannot be explained by the patient's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and volanesorsen administration
- **Unlikely/Remote:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to volanesorsen administration and/or exposure suggests that a causal relationship is unlikely (For reporting purposes, Unlikely/Remote will be grouped together with Not Related)
- **Not Related:** The event can be readily explained by the patient's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and volanesorsen

9.4.3.2 Severity

The severity of AEs and SAEs will be graded based on criteria from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010 (refer to Appendix D). Any AE not listed in Appendix D will be graded as follows:

- **Mild:** The event is easily tolerated by the patient and does not affect the patient's usual daily activities
- **Moderate:** The event causes the patient more discomfort and interrupts the patient's usual daily activities
- **Severe:** The event is incapacitating and causes considerable interference with the patient's usual daily activities

If the event is an SAE, then all applicable seriousness criteria must be indicated (criteria listed in Section 9.3.3).

9.4.3.3 Action Taken with Volanesorsen

Action taken with volanesorsen due to the event is characterized by 1 of the following:

- **None:** No changes were made to volanesorsen administration and dose
- **Permanently Discontinued:** Volanesorsen was discontinued and not restarted
- **Temporarily Interrupted, restarted – same dose:** Dosing was temporarily interrupted or delayed due to the AE and restarted at the same dose
- **Reduced schedule:** Dosing frequency was reduced

9.4.3.4 Treatment Given for Adverse Event

Any treatment (e.g., medications or procedures) given for the AE should be recorded on the Adverse Event Case Report Form (treatment should also be recorded on the concomitant treatment or ancillary procedures CRF as appropriate).

9.4.3.5 Outcome of the Adverse Event

If the event is a non-serious AE then the event's outcome is characterized by 1 of the following:

- **AE Persists:** Patient terminates from the trial and the AE continues
- **Recovered:** Patient recovered completely from the AE
- **Became Serious:** The event became serious (the date that the event became serious should be recorded as the Resolution Date of that AE and the Onset Date of the corresponding SAE)
- **Change in Severity** (if applicable): AE severity changed

If the event is a SAE then the event's outcome is characterized by 1 of the following:

- **Ongoing:** SAE continuing
- **Persists (as non-serious AE):** Patient has not fully recovered but the event no longer meets serious criteria and should be captured as an AE on the non-serious AE eCRF (the SAE resolution date should be entered as the date of onset of that AE)

- **Recovered:** Patient recovered completely from the SAE (the date of recovery should be entered as the SAE resolution date)

- **Fatal:** Patient died (the date of death should be entered as the SAE resolution date)

9.4.4 Adjudication Committees

All SAEs that occur during the study that are consistent with a major acute cardiovascular event (MACE) will be adjudicated by a blinded, independent committee as outlined in the MACE Adjudication Charter.

All AEs and SAEs that occur during the study that are consistent with an event of acute pancreatitis will be adjudicated by a blinded, independent committee according to the Atlanta classification of acute pancreatitis (Banks et al. 2013) and as outlined in the Pancreatitis Adjudication Charter. In addition, data for prior episodes of acute pancreatitis or suspected pancreatitis will be collected by review of each patient's medical chart and these events will also be adjudicated.

9.5 Procedures for Handling Special Situations

9.5.1 Abnormalities of Laboratory Tests

Clinically-significant abnormal laboratory test results may, in the opinion of the Investigator, constitute or be associated with an AE. Examples of these include abnormal laboratory results that are associated with symptoms, or require treatment, e.g., bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac arrhythmias due to hyperkalemia. Whenever possible, the underlying diagnosis should be listed in preference to abnormal laboratory values as AEs. Clinically-significant abnormalities will be monitored by the Investigator until the parameter returns to its baseline value or until agreement is reached between the Investigator and Sponsor Medical Monitor. Laboratory abnormalities deemed not clinically-significant (NCS) by the Investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator should not be deemed NCS on the laboratory sheet.

The Investigator is responsible for reviewing and signing all laboratory reports. The signed clinical laboratory reports will serve as source documents and should include the Investigator's assessment of clinical significance of out of range/abnormal laboratory values.

9.5.2 Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the patient is hospitalized; the Study Center must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the patient's consent to participate in the study

- The condition that required the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the patient's consent to participate in the study and the timing of the procedure or treatment

- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission

9.5.3 Dosing Errors

Volanesorsen dosing errors should be documented as Protocol Deviations. A brief description should be provided in the deviation, including whether the patient was symptomatic (list symptoms) or asymptomatic, and the event accidental or intentional.

Dosing details should be captured on the Dosing Case Report Form. If the patient takes a dose of volanesorsen that exceeds protocol specifications and the patient is symptomatic, then the symptom(s) should be documented as an AE and be reported per Section 9.4.

Should an overdose occur, the Investigator or designee should refer to the Guidance to Investigator's section of the Investigator's Brochure and contact the Sponsor or designee within 24 hours.

9.5.4 Contraception and Pregnancy

Male patients and female patients of childbearing potential must continue to use appropriate contraception with their partners, or refrain from sexual activity, as described in Section 6.3.1.

If a patient becomes pregnant or a pregnancy is suspected, or if a male patient makes or believes that he has made someone pregnant during the study, then the Study Center staff must be informed immediately. An Initial Pregnancy Form should be submitted to the Sponsor or designee **within 24 hours** of first learning of the occurrence of pregnancy. Follow-up information including delivery or termination is reported on Follow-up Pregnancy Forms and reported within 24 hours.

Payment for all aspects of obstetrical care, child or related care will be the patient's responsibility.

Female patients: If a suspected pregnancy occurs while on the study (including follow-up), a pregnancy test will be performed. The patient with a confirmed pregnancy will be immediately withdrawn from treatment with volanesorsen. However, the patient will be encouraged to complete the post-treatment follow-up portion of the study to the extent that study procedures do not interfere with the pregnancy. Regardless of continued study participation, the study physician will assist the patient in getting obstetrical care and the progress of the pregnancy will be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the Study Center and Sponsor may require access to the mother and infant's medical records for an additional 8 weeks after birth.

Male patients: The progress of the pregnancy in a male patient's partner should be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, **the Study Center and Sponsor may request access to the mother and infant's medical records for an additional 8 weeks after birth**. Follow-up will be performed to the extent permitted by applicable regulations and privacy considerations.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints

For fasting lipid measurements, the values at Month 3 analysis time point are defined as the average of Week 12 (Day 78) and Week 13 (Day 85) fasting assessments, the values of Month 6 analysis time point is at the end of Month 6 are defined as the average of Week 25 (Day 169) and Week 26 (Day 176) fasting assessments, and the values at the Month 12 analysis time point are defined as the average of Week 50 (Day 344) and Week 52 (Day 358) fasting assessments.

10.1.1 Efficacy Endpoints

- Percent change and absolute change from baseline in fasting TG
- Frequency and severity of patient reported abdominal pain during the treatment period
- Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-HDL-C, apoB, HDL-C, apolipoprotein A-1 (apoA-1), VLDL-C, and LDL-C
- Percent change from baseline in fasting total apolipoprotein C-III
- Quality of Life questionnaires (EQ-5D, SF-36)
- Adjudicated acute pancreatitis event rate
- Other symptoms: eruptive xanthoma, lipemia retinalis

10.1.2 Safety Endpoints

- Adverse events including adjudicated events of pancreatitis and MACE
- Vital signs and weight
- Physical examinations
- Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis)
- Echocardiography
- Electrocardiograms (ECGs)
- Use of concomitant medications
- MRIs

10.2 Sample Size

No sample size calculations were performed as this is an open-label study.

10.3 Populations

Full Analysis Set (FAS): All patients who are enrolled and have a baseline TG assessment. The FAS represents the practically-feasible intent-to-treat (ITT) population as delineated in ICH Guideline E9.

Per Protocol Set (PPS): Subset of the FAS who received 9 of first 13 scheduled doses of volanesorsen and with no significant protocol deviations that would be expected to affect efficacy and PD assessments. The detailed criteria will be specified and finalized prior to the final database lock.

Safety Set: All patients who are enrolled and receive at least 1 dose of volanesorsen.

PK Population: All patients who are enrolled, receive at least 1 dose of volanesorsen, and have at least 1 evaluable PK sample collected, analyzed, and reported.

10.4 Definition of Baseline

Definitions of baseline are given below for the purposes of the final analysis.

For fasting lipid measurements, 2 baselines are defined for each patient in Groups 1 and 2: Group 1 (ISIS 304801-CS6) or Group 2 (ISIS 304801-CS16) index study baseline and the baseline in this open-label study, which is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 (e.g., qualification assessments or assessments from final visit of the ISIS 304801-CS6 or ISIS 304801-CS16 index studies if used for qualification).

For other measurements, baseline for patients on active treatment in the ISIS 304801-CS6 or ISIS 304801-CS16 index study will be the ISIS 304801-CS6 or ISIS 304801-CS16 index study baseline. For patients on placebo in the ISIS 304801-CS6 or ISIS 304801-CS16 index study, baseline for safety will be the last non-missing assessment prior to the first dose of Study Drug.

10.5 Interim Analysis

An interim analysis may be conducted after the last patient's Week 13 visit of the open-label study or after the database of the ISIS 304801-CS6 and ISIS 304801-CS16 index studies are locked and unblinded. Both safety and efficacy information from this open-label study may be summarized during this interim analysis. Efficacy analyses will be detailed in the SAP.

10.6 Planned Methods of Analysis

All eCRF data, lab data transfers, as well as any outcomes derived from the data, will be provided in the patient data listings. Patient data listings will be presented for all patients enrolled into the study. Descriptive summary statistics including n, mean, median, standard deviation, standard error, interquartile range (25th percentile, 75th percentile), and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data by treatment group. Where appropriate, p-values will be reported. All statistical tests will be conducted using 2-sided tests with 5% Type I error rates unless otherwise stated.

All efficacy endpoints will be assessed in the FAS and PPS. All safety assessments will be performed on the Safety Set. PK endpoints will be assessed in the PK Set as applicable.

10.6.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics by treatment group. The patient disposition will be summarized by treatment group of the index studies. All patients enrolled will be included in a summary of patient disposition.

10.6.2 Safety Analysis

Treatment duration and amount of Study Drug received will be summarized by treatment group of the index studies.

Patient incidence rates of AEs will be tabulated by MedDRA system organ class, MedDRA preferred term, and treatment group of the index studies. Narratives of treatment-emergent deaths, serious and significant AEs, including early withdrawals due to AEs, will also be provided.

All treatment-emergent AEs, all treatment-emergent AEs potentially related to Study Drug, all treatment-emergent serious AEs, and all treatment-emergent serious AEs potentially related to Study Drug will be summarized.

Injection Site Reactions (ISRs) will be summarized by treatment group of the index studies, MedDRA preferred term and severity.

Independently adjudicated events of MACE and pancreatitis will be summarized by treatment group of the index studies.

Laboratory tests to ensure patient safety including chemistry panel, complete blood count (CBC) with differential, coagulation panel, IM, complement etc., will be summarized by study visits by treatment group of the index studies.

These safety variables will also be presented as change and percent change from baseline over time after Study Drug administration, as appropriate.

Vital signs, weight, ECG measures, echocardiography assessments, and MRI assessments will be tabulated by treatment group of the index studies.

10.6.3 Efficacy Analysis

Percent change and change from baseline to Month 3, Month 6, and Month 12 in fasting TG will be summarized by treatment group of the index studies. Response rate of patients with fasting plasma TG < 750 mg/dL or achieving fasting TG $\geq 40\%$ reduction from baseline at Month 3, Month 6, and Month 12 will be summarized. Response analysis will also be conducted using a range of fasting plasma TG thresholds for determination of responder status.

Percent change and change from baseline to Month 3, Month 6, and Month 12 will also be summarized by treatment group of the index studies for other fasting lipid measures including non-HDL-C, apoB, HDL-C, apoA-1, VLDL-C, and LDL-C, total cholesterol, and fasting total apoC-III.

The incremental effects of volanesorsen on lipid measures will be explored and the association between changes in lipid parameters and total amount of drug received will be examined, as appropriate.

Frequency and severity of patient reported abdominal pain, adjudicated acute pancreatitis event rate, quality of life assessments, and comparison of other symptoms including eruptive xanthomas and lipemia retinalis will be summarized by treatment group of the index studies.

Additional details of the analyses to be conducted will be provided in the SAP.

10.6.4 Pharmacokinetic and Immunogenicity Analysis

10.6.4.1 Pharmacokinetic Analysis

For all patients, pre-dose and post-treatment volanesorsen plasma concentrations will be summarized using descriptive statistics, with stratification for Group 1 and 2 patients by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16 and IM status.

For patients in the PK subgroup only, non-compartmental PK analysis of volanesorsen will be carried out on each individual patient data set using data collected in the open-label study from the intensive PK subgroup, following a single-dose (i.e., single-dose PK) or multiple doses (i.e., steady-state PK), depending on their earlier treatment in the index studies (Group 1 and 2 patients). On Week 1 Day 1 of the open-label study, patients who received placebo in the index study (and all patients in Group 3) will receive the first treatment of volanesorsen (single-dose PK), while patients who received volanesorsen in the index studies had been on volanesorsen treatment for 12 months (ISIS 304801-CS6) or 6 months (ISIS 304801-CS16), thus the PK data collected from these patients reflect steady-state PK. The maximum observed drug concentration (C_{max}) and the time taken to reach C_{max} (T_{max}) will be obtained directly from the concentration-time data. Area under the plasma concentration-time curve from time zero to 24 hours ($AUC_{0\text{-}24hr}$) will be calculated using the linear trapezoidal rule. Apparent systemic (plasma) clearance after SC administration ($CL_{0\text{-}24hr}/F_{0\text{-}24hr}$) will be calculated from $CL_{0\text{-}24hr}/F_{0\text{-}24hr}$ = Actual Dose/$AUC_{0\text{-}24hr}$. Mean residence time (MRT) from time zero to 24 hours after the SC administration will be calculated from the equation, $MRT_{0\text{-}24hr} = AUMC_{0\text{-}24hr}/AUC_{0\text{-}24hr}$, where $AUMC_{0\text{-}24hr}$ is the area under the moment plasma concentration-time curve from time zero to 24 hours after the SC administration. Other PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist.

Plasma PK parameters will be summarized using descriptive statistics, with and without stratification by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16 and IM status. Additional details regarding the PK analysis will be described in the SAP.

Population PK, PK/PD, and covariate analysis may be performed if deemed appropriate, and results will be reported separately.

10.6.4.2 Immunogenicity Analysis

Immunogenicity (IM) results (screen positive/negative, confirmed positive/negative or not evaluable, and when applicable, titer of anti-volanesorsen antibodies) before, during, and after treatment with Study Drug (volanesorsen) (i.e., sample [anti-drug antibody] ADA status) will be

listed by their prior treatment in study ISIS 304801-CS6 or ISIS 304801-CS16 (Groups 1 and 2) and study day. Subject ADA status (positive/negative or not evaluable) for all evaluable patients, along with the study day associated with the first positive IM status emerged (T_{first}, i.e., onset of ADA development), the last positive IM status observed (T_{last}), the duration of ADA response (number of days between T_{first} and T_{last}) if appropriate, the last ADA sample collection day, and subject - peak titer if applicable, will be listed by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16 (Groups 1 and 2) and study day. Subjects with positive anti-volanesorsen antibody status may be further classified (when applicable) as being either 'persistent', 'transient', or 'not determinable', if deemed appropriate.

Additionally, the sample and subject IM incidence (number) and incidence rate (percent) will be summarized as the total number and percent of evaluated subjects with antibody negative, positive, and unknown status by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16. Furthermore, onset, duration, and titer of the ADA response, if applicable, will be summarized as median, quartiles (25% and 75%), and range.

Additional details regarding the IM data analysis will be described in the SAP.

Potential relationships between immunogenicity results (e.g., IM status) and selected efficacy (e.g., % change in fasting TG from baseline at 3-, 6-, and 12-month endpoints), safety, and PK (e.g., C_{trough}) measures will be evaluated using graphical analysis and statistical analysis. These analyses will be either conducted and included in the study report, or data pooled and analyzed from all available Phase 2 and 3 studies and reported separately.

11. INVESTIGATOR'S REGULATORY OBLIGATIONS

11.1 Informed Consent

The written informed consent document should be prepared in the language(s) of the potential patient population, based on an English version provided by the Sponsor.

Before a patient's participation in the trial, the Investigator is responsible for obtaining written informed consent from the patient after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific qualification procedures or any Study Drug are administered. The patient must be given sufficient time to consider whether to participate in the study.

The acquisition of informed consent and the patient's agreement or refusal to notify his/her primary care physician should be documented in the patient's medical records and the informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion (not necessarily an Investigator). The original signed informed consent form should be retained in the Study Master File and in any other locations required by institutional policy, and a copy of the signed consent form should be provided to the patient.

11.2 Ethical Conduct of the Study

The Guidelines of the World Medical Association (WMA) Declaration of Helsinki dated October 2002 the applicable regulations and guidelines of current Good Clinical Practice (GCP) as well as the demands of national drug and data protection laws and other applicable regulatory requirements will be strictly followed.

11.3 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent form, other written patient information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by the Sponsor before recruitment of patients into the study and shipment of volanesorsen. A copy of the written approval of any other items/materials that must be approved by the Study Center or IEC/IRB must also be received by the Sponsor before recruitment of patients into the study and shipment of Study Drug. The Investigator's Brochure must be submitted to the IEC/IRB for acknowledgement.

The Investigator must submit to and, where necessary, obtain approval from the IEC/IRB, for all subsequent protocol amendments and changes to the informed consent document. The Investigator should notify the IEC/IRB of deviations from the protocol in accordance with ICH GCP Section 4.5.2. The Investigator should also notify the IEC/IRB of serious adverse events occurring at the Study Center and other adverse event reports received from the Sponsor, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study. Copies of the Investigator's reports, all IEC/IRB submissions and the IEC/IRB continuance of approval must be sent to the Sponsor.

11.4 Patient Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained. On the case report forms (CRF) or other documents submitted to the Sponsor, patients should be identified by unique initials and a patient study number only. Documents that are not for submission to the Sponsor (e.g., signed informed consent forms) should be kept in strict confidence by the Investigator.

In compliance with Federal and local regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the patient to permit named representatives to have access to his/her study-related records without violating the confidentiality of the patient.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments

Protocol amendments must be made only with the prior approval of the Sponsor. Agreement from the Investigator must be obtained for all protocol amendments and amendments to the informed consent document. The regulatory authority and IEC/IRB must be informed of all amendments and give approval for any amendments likely to affect the safety of the patients or the conduct of the trial. The Investigator **must** send a copy of the approval letter from the IEC/IRB to the Sponsor.

12.2 Study Termination

The Sponsor reserves the right to terminate the study according to the terms of the site contract. The Investigator reserves the right to terminate their participation in the study, according to the terms of the site contract. The Investigator/Sponsor should notify the IEC/IRB in writing of the trial's completion or early termination and send a copy of the notification to the Sponsor.

12.3 Study Documentation and Storage

An electronic case report form (eCRF) utilizing an Electronic Data Capture (EDC) application will be used for this study.

The Investigator should ensure that all appropriately qualified persons to whom he/she has delegated trial duties are recorded on a Sponsor-approved Delegation of Site Responsibilities Form.

Source documents are original documents, data, and records from which the patient's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, imaging, and correspondence. In this study, CRFs may not be used as source documents.

The Investigator and Study Center staffs are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation in accordance with Section 8 of the ICH Guidelines (E6), suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Elements should include:

- Patient files containing completed CRFs, informed consents, and supporting copies of source documentation
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation and all correspondence to and from the IEC/IRB and the Sponsor
- If volanesorsen supplies are maintained at the Study Center, proof of receipt, volanesorsen Accountability Record, Return of volanesorsen for Destruction, final study volanesorsen reconciliation, and all volanesorsen-related correspondence

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

No study document should be destroyed without prior written agreement between the Sponsor or and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor.

12.4 Study Monitoring

The Sponsor representative and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the trial (e.g., CRFs and other pertinent data) provided that patient confidentiality is respected.

The Sponsor monitor is responsible for inspecting the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to patient medical records and other study-related records needed to verify the entries on the CRFs.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's Clinical Quality Assurance Department. Inspection of Study Center facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the trial conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

To ensure the quality of clinical data a clinical data management review will be performed on patient data received by the Sponsor. During this review, patient data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or Study Center notifications will be sent to the Study Center for completion and return to Sponsor.

The Principal Investigator will sign and date the indicated places on the CRF. These signatures will indicate that the principal Investigator inspected or reviewed the data on the CRF, the data queries, and the Study Center notifications, and agrees with the content.

12.5 Language

Case report forms must be completed in English. Generic names for concomitant medications should be recorded in English if possible, unless it is a combination drug, then record the trade name in English.

All written information and other material to be used by patients and investigative staff must use vocabulary and language that are clearly understood.

12.6 Compensation for Injury

The Sponsor maintains appropriate insurance coverage for clinical trials and will follow applicable local compensation laws. Patients will be treated and/or compensated for any study-related illness/injury in accordance with the information provided in the Compensation for Injury section of the Informed Consent document.

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14. APPENDICES

Appendix A Schedule of Procedures

Appendix A Schedule of Procedures

Study Period		Screen/ Run In[a]	Qual[a]	Treatment Period																							Post Treatment Follow-up		
Study Week		-8 to -2	-2 to -1	Wk 1		Wk 2.5	Wk 4	Wk 6	Wk 8	Wk 10	Month 3		Wk 15 & 17	Wk 19	Wk 21 & 23	Month 6		Wk 28 & 30	Wk 32	Wk 34 & 36	Wk 38	Wk 40 & 42	Wk 44	Wk 46 & 48	Month 12		Wk 54 & 56	Wk 58	Wk 65
											Wk 12	Wk 13				Wk 25	Wk 26								Wk 50	Wk 52 or ET			
Study Day		-56 to -15	-14 to -7	1	2	11	22	36	50	64	78	85	99 & 113	127	141 & 155	169	176	190 & 204	218	232 & 246	260	274 & 288	302	316 & 330	344	358	372 & 386	400	449
Visit Window+/- Days		0	0	0	0	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	7	7
Informed Consent		X	X																										
Outpatient Visit		X	X	X	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X	X[j]	X[j]	X[j]	X[j]	X	X[j]	X[j]	X[j]	X	X[j]	X[j]	X[j]	X[j]	X	X[j]	X[j]	X
Inclusion/Exclusion Criteria		X	X																										
Vital Signs + body weight (+ height on Day 1 only)		X	X	X			X		X			X					X				X					X			X
Physical Examination		X	X	X								X					X				X					X			X
12- lead ECG (triplicate)		X	X									X					X				X					X			X
MRI (liver/spleen)		X																								X[k]			
Echocardiography		X															X[k]									X[k]			
Blood Draw (Fasting)[c]	Chemistry Panel	X	X	X			X		X			X		X			X		X		X		X				X		X	X
	CBC with Differential[b]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Serum Lipid Panel	X	X	X			X		X		X	X				X	X				X				X	X			X
	Coagulation (aPTT, PT, INR)	X	X						X			X					X				X					X			
	hsCRP, HbA1c, FPG, and de-lipidated free glycerol	X[n]	X[n]	X								X					X									X			X
	Sedimentation Rate			X								X					X									X			X
	Complement (C5a, Bb)			X								X					X									X			X
	Plasma PK - Volanesorsen			X[l]	X		X		X			X					X				X					X			X
	Anti-Volanesorsen Antibodies			X			X		X			X					X				X					X			X
	FSH (women only, if applicable)	X	X																										
	Serum Pregnancy Test[d]	X	X				X		X			X		X			X		X		X		X			X		X	X
	Archived Serum & Plasma Samples[e]			X					X			X					X									X			X
	Troponin I[o]	X	X																										

Appendix A Schedule of Procedures *Continued*

Study Period	Screen/ Run In[a]	Qual[a]	Treatment Period																								Post Treatment Follow-up		
Study Week	-8 to -2	-2 to -1	Wk 1		Wk 2.5	Wk 4	Wk 6	Wk 8	Wk 10	Month 3		Wk 15 & 17	Wk 19	Wk 21 & 23	Month 6		Wk 28 & 30	Wk 32	Wk 34 & 36	Wk 38	Wk 40 & 42	Wk 44	Wk 46 & 48	Month 12		Wk 54 & 56	Wk 58	Wk 65
										Wk 12	Wk 13				Wk 25	Wk 26								Wk 50	Wk 52 or ET			
Study Day	-56 to -15	-14 to -7	1	2	11	22	36	50	64	78	85	99 & 113	127	141 & 155	169	176	190 & 204	218	232 & 246	260	274 & 288	302	316 & 330	344	358	372 & 386	400	449
Visit Window+/- Days	0	0	0	0	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	7	7
Urinalysis[c]	X	X	X[m]			X		X			X[m]		X[m]			X[m]		X[m]		X[m]		X[m]			X[m]		X[m]	X[m]
Fundus Photography[f]	X																								X[k]			
Genetic testing for FCS diagnosis (if not available in medical history)[g]	X																											
Weekly Study Drug: SC Injection			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Symptom Diary (weekly)	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Assessment(s)			X								X					X									X			X
Food/Drink Diary (quarterly)[h]			X								X					X									X			X
Diet/Alcohol Counseling[i]	X	X	X			X		X			X					X				X					X		X	X
Adverse Events	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a Screening (Group 3) and Qualification procedures performed (Please refer to Sections 3.4, 4.1, and 6.1.2)

b Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1-week and determined not to have met a stopping rule before dosing can continue. If there is no reportable platelet count within 14 days of the last platelet count, the Investigator will contact the patient to hold dosing until a new platelet count is obtained and reviewed. All platelet count results will be promptly reviewed by the Investigator to ensure that the count has not met the stopping rule and to determine whether the rate of decline is suggestive that the patient could be approaching the dose pause rule of 75,000/mm^3. In the event of any platelet count less than 50,000/mm^3 or a rate of decline ≥ 50% between two consecutive assessments, irrespective of the platelet level, then dosing of a patient with Study Drug (ISIS 304801 or placebo) will be stopped permanently. Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor

Appendix A Schedule of Procedures Continued

Legend Text *Continued*

c Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours. During treatment period urine and blood samples will be collected prior to Study Drug administration. Does not apply to 24-hour PK blood draw

d Females of childbearing potential only

e Serum and plasma samples will be collected and stored for follow-up exploration of laboratory findings and/or adverse events (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.) in this or subsequent clinical studies of volanesorsen

f If possible, fundus photography should be completed prior to administration of the first dose of Study Drug (Group 2 [ISIS 304801-CS16 rollover patients] and Group 3) and repeated at Week 52 (Please refer to Section 6.2.2.2)

g Genetic testing can be conducted for study qualification (Group 2 [ISIS 304801-CS16 rollover patients] and Group 3); genetic testing will only be conducted if allowed in the geographic region and only after the patient has given specific written informed consent for genetic testing

h In addition to diary, patients will be contacted at random times during the study to review their current eating and drinking habits

i To reinforce compliance to the diet and alcohol restrictions. Random diet/alcohol assessments (phone visits) will also be performed by dietician or study personnel

j Assessments and procedures to be conducted by either a home healthcare nurse, or the Study Center as arranged by the Study Center personnel

k A ± 7-day window is allowed for MRI, echocardiography procedures and fundus photography

l Full or abbreviated PK profile (see Appendix C)

m Expanded urinalysis (see Appendix B)

n HbA1c only

o All abnormal troponin samples will be rerun at the central laboratory and also analyzed for CK-MB

Appendix B List of Laboratory Analytes

Appendix B List of Laboratory Analytes

Based on emerging data from this or future studies, additional tests not listed below may be performed on stored samples to better characterize the profile of volanesorsen or other similar oligonucleotides.

Clinical Chemistry Panel

- Sodium
- Potassium
- Chloride
- Bicarbonate
- Total protein
- Albumin
- Calcium
- Magnesium
- Phosphorus
- Glucose
- BUN
- Creatinine
- Uric Acid
- Total bilirubin
- Direct (conjugated) bilirubin
- Indirect (unconjugated) bilirubin
- ALT
- AST
- Alkaline phosphatase

Coagulation

- aPTT (sec)
- PT (sec)
- INR

Lipid Panel

- Total Cholesterol
- LDL-C
- HDL-C
- Triglycerides
- Non-HDL-C
- VLDL-C
- apoA-1
- apoB
- apoC-III

Hematology

- Red blood cells
- Hemoglobin
- Hematocrit
- MCV, MCH, MCHC
- Platelets
- White blood cells
- WBC Differential (% and absolute)
  - Neutrophils
  - Eosinophils
  - Basophils
  - Lymphocytes
  - Monocytes

Pharmacokinetics[1] & Immunogenicity

- Volanesorsen levels in plasma
- Anti-volanesorsen antibodies in plasma

Other Assessments

- hsCRP
- Sedimentation Rate
- C5a, Bb
- De-lipidated free glycerol
- HbA1c, FPG

Urinalysis

- Color
- Appearance
- Specific gravity
- pH
- Protein
- Blood
- Ketones
- Urobilinogen
- Glucose
- Bilirubin
- Leukocyte esterase
- Nitrate
- Microscopic examination[2]

Additional Measures for Expanded Urinalysis

- Total protein (quantitative)
- Microalbumin
- β2-microglobulin

1 Plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, IM testing (or possibly for purposes of IM assay development and/or validation), or to assess other actions of volanesorsen with plasma constituents

2 Will be performed on abnormal findings unless otherwise specified

Appendix C Pharmacokinetic Sampling Schedule

Appendix C Pharmacokinetic Sampling Schedule

Blood samples for the determination of plasma volanesorsen concentrations will be collected prior to dosing, and at various times throughout the dosing and post-treatment follow-up period as noted in the tables below.

PK Sampling Schedule (All Patients except PK Subgroup)

Week	Wk 1	Wk 4	Wk 8	Wk 13	Wk 26	Wk 38	Wk 52	Wk 65
Study Day	**D1**	**D22**	**D50**	**D85**	**D176**	**D260**	**D358**	**D449**
Visit Window +/- Days	0	2	2	2	2	3	2	7
Time Point	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime

PK Sampling Schedule (PK Subgroup only*)

Week	Wk 1	Wk 1	Wk 4	Wk 8	Wk 13	Wk 26	Wk 38	Wk 52	Wk 65
Study Day	**D1**	**D2**	**D22**	**D50**	**D85**	**D176**	**D260**	**D358**	**D449**
Visit Window +/- Days	0	0	2	2	2	2	3	2	7
Time Point	Pre-dose, 1, 2, 3, 4, 6, 8, and 12 hrs post-dose	24 hrs post-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime

* Patients at selected sites will be asked to participate in the extended 24-hour PK profile beginning on Study Day 1. Participation is optional

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

The following grading recommendations for adverse events relating to lab test abnormalities are based upon the **Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010**

Adverse Event	Mild	Moderate	Severe
Hematology			
aPTT prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage
Eosinophils increased†	650 – 1,500 cell/mm^3	1,501 - 5,000 cell/mm^3	>5,000 cell/mm^3
Fibrinogen decreased	<1.0 - 0.75 x LLN or <25% decrease from baseline	<0.75 - 0.5 x LLN or 25 - <50% decrease from baseline	<0.5 x LLN or ≥50% decrease from baseline
Hemoglobin decreased (Anemia)	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated
Hemoglobin increased	Increase in >0 - 2 g/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 g/dL above ULN or above baseline if baseline is above ULN	Increase in >4 g/dL above ULN or above baseline if baseline is above ULN
INR increased	>1 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation
Lymphocyte count decreased	<LLN - 800/mm^3; <LLN - 0.8 x 10^9/L	<800 - 500/mm^3; <0.8 - 0.5 x 10^9 /L	<500 /mm^3; <0.5 x 10^9 /L
Lymphocyte count increased	-	>4000/mm^3 - 20,000/mm^3	>20,000/mm^3
Neutrophil count decreased	<LLN - 1500/mm^3; <LLN - 1.5 x 10^9 /L	<1500 - 1000/mm^3; <1.5 - 1.0 x 10^9 /L	<1000/mm^3; <1.0 x 10^9 /L
Platelet count decreased	<LLN - 75,000/mm^3; <LLN - 75.0 x 10^9 /L	<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9 /L	<50,000/mm^3; <50.0 x 10^9 /L
White blood cell decreased	<LLN - 3000/mm^3; <LLN - 3.0 x 10^9 /L	<3000 - 2000/mm^3; <3.0 - 2.0 x 10^9 /L	<2000/mm^3; <2.0 x 10^9 /L
Chemistry			
Acidosis	pH <normal, but >=7.3	-	pH <7.3
Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Alkalosis	pH >normal, but ≤7.5	-	pH >7.5
Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 x ULN
Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

Adverse Event	Mild	Moderate	Severe
Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer
CD4 lymphocytes decreased	<LLN - 500/mm^3; <LLN - 0.5 x 10^9 /L	<500 - 200/mm^3; <0.5 - 0.2 x 10^9 /L	<200/mm^3; <0.2 x 10^9 /L
CPK increased*	>ULN - <6 ULN	6 - 10 x ULN	>10 x ULN
Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 x ULN
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 mg/dL; >3.1 mmol/L; Ionized calcium >1.6 mmol/L; hospitalization indicated
Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 mg/dL; >13.9 mmol/L; hospitalization indicated
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0; hospitalization indicated
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 mg/dL; >1.23 mmol/L
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 mmol/L; hospitalization indicated
Hyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 mg/dL; <1.75 mmol/L; Ionized calcium <0.9 mmol/L; hospitalization indicated
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 mg/dL; <3.0 mmol/L	<40 mg/dL (<2.2 mmol/L) AND requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions‡
Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 mmol/L; hospitalization indicated
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 mg/dL; <0.4 mmol/L
Hyponatremia	<LLN - 130 mmol/L	-	<130 mmol/L
Hypophosphatemia	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 mg/dL; <0.6 mmol/L
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

Adverse Event	Mild	Moderate	Severe
Urine			
Proteinuria Adults Children	1+ proteinuria; urinary protein <1.0 g/24 hrs -	2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs; Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Urinary protein ≥3.5 g/24 hrs; Urine P/C >1.9
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated

†Grading for this parameter is derived from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007

*Grading for this parameter is derived from the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0, Nov 2014

‡Modified for consistency with the ADA and Endocrine Society Guidelines (Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. Diabetes Care 2013;36:1384-95)

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ISIS 304801-CS7

The APPROACH Open-Label Study

Volanesorsen (ISIS 304801)

An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol Amendment 5 – 6 July 2016

EudraCT No: 2015-003755-21

ISIS 304801-CS7

The APPROACH Open-Label Study

Volanesorsen (ISIS 304801)

An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol Amendment 5 – 6 July 2016

Protocol History:

Original Protocol:	28 August 2015
Protocol Amendment 1:	2 February 2016
Protocol Amendment 2:	22 April 2016
Protocol Amendment 3:	9 May 2016
Protocol Amendment 4:	6 June 2016

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Ionis Protocol Number: ISIS 304801-CS7

Protocol Amendment 5

EudraCT No: 2015-003755-21

Clinical Phase: 3

The APPROACH Open-Label Study

Volanesorsen (ISIS 304801)

An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

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Date: 6 July 2016

Confidentiality Statement

This document contains confidential information of Ionis Pharmaceuticals, Inc., that must not be disclosed to anyone other than the recipient study staff and members of the independent ethics committee, institutional review board, or authorized regulatory agencies. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc.

Protocol Signature Page

Protocol Number:	ISIS 304801-CS7
Protocol Title:	An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Amendment:	Amendment 5
Date:	6 July 2016

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)", dated 6 July 2016, and agree to conduct the study as described herein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice (E6).

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc.

Investigator's Signature

Investigator's Name *(please print)* Date (DD Month YYYY)

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PROTOCOL AMENDMENT

Protocol Number:	ISIS 304801-CS7
Protocol Title:	An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Amendment Number:	5
Amendment Date:	6 July 2016

The purpose of this protocol amendment is to implement the following modifications to Protocol ISIS 304801-CS7 Amendment 4 dated 6 June 2016:

1. To enroll FCS patients in this open label study who did not participate in the ISIS 304801–CS6 or ISIS 304801–CS16 index studies.

   For clarity, the protocol now specifies 3 patient groups, with assignment based on prior involvement in index studies of ISIS 304801:

   Group 1: ISIS 304801-CS6 (index study) rollover FCS patients

   Group 2: ISIS 304801-CS16 (index study) rollover FCS patients

   Group 3: FCS patients who did not participate in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies

2. To remove language that indicates that lipoprotein lipase (LPL) activity can be measured if needed for study qualification for patients in Groups 2 and 3.
3. To add language to indicate that a second Study Drug rechallenge will not be allowed following a platelet count decrease below 75,000/mm^3.
4. To provide clarifications to the platelet safety monitoring rules in Table 2.
5. To add language to indicate that patients who discontinue early from Study Drug, or the study, should be followed as per the platelet monitoring rules shown in Table 2 for the first 6 weeks after discontinuing Study Drug and the next platelet count should be taken within at least 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug.

Minor changes (not included in the list of changes below) have been made throughout the protocol to correct errors and/or to improve the overall clarity of the original protocol but these changes do not impact subject safety, exposure, or the overall study design.

The following table provides a summary list of major changes to the protocol:

Protocol Section	Description of Change	Rationale
Protocol Title pages Signature page Protocol Synopsis: Title, Study Population, Rationale for Dose and Schedule Selection, Study Visit Schedule and Procedures, Statistical Considerations 5.1 Inclusion Criteria	"Extension" was removed from the study title	To note that FCS patients who did not participate in an index study will also be enrolled
Protocol Synopsis: Study Design 3.1 Study Design	**Was:** This is a multi-center open-label extension study of ISIS 304801-CS6 and ISIS 304801-CS16 **Is:** This is a multi-center open-label study of: Group 1: ISIS 304801-CS6 (index study) roll over FCS patients Group 2: ISIS 304801-CS16 (index study) roll over FCS patients Group 3: FCS patients who did not participate in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies	To distinguish patients who participated in an index study from those who did not
Protocol Synopsis: Study Population 5.1 Inclusion Criteria	**Was:** 3. Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement. Patients who are enrolled in ISIS 304801-CS16 must also meet the following criteria in order to enter into the Extension Study: a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L) b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) by documentation of at least 1 of the following: • Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1) • Post heparin plasma LPL activity of ≤ 20% of normal c. Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 study	To define the inclusion criteria for each Group of patients LPL removed to avoid the production of heparin induced anti-platelet antibodies

Protocol Section	Description of Change	Rationale
Protocol Synopsis: Study Population *Continued* 5.1 Inclusion Criteria *Continued*	**Is:** *Continued* 3. Groups 1 and 2: Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement. Groups 2 and 3: Patients must also meet the following criteria in order to enter into the open-label study: a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L) b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) by documentation of the following: • Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1) c. Group 2: Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 index study Group 3: Fasting TG ≥ 750 mg/dL at Screening for this open-label study	To define the inclusion criteria for each Group of patients LPL removed to avoid the production of heparin induced anti-platelet antibodies *Continued*
Protocol Synopsis: Study Population 5.2 Exclusion Criteria	**Was:** **Exclusion Criteria** 1. Have any new condition or worsening of existing condition which in the opinion of the Investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study 2. Unwilling to comply with lifestyle requirements for the duration of the study (Section 6.3) **Is:** **Exclusion Criteria for Group 1 (ISIS 304801-CS6) and Group 2 (ISIS 304801-CS16) Index Study Roll-over Patients** 1. Have any new condition or worsening of existing condition which in the opinion of the Investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study 2. Unwilling to comply with lifestyle requirements for the duration of the study (Section 6.3) **Exclusion Criteria for Group 3 (patients who did not participate in an index study)** 1. Diabetes mellitus with any of the following: a. Newly diagnosed within 12 weeks of screening b. HbA1c ≥ 9.0% at Screening c. Recent change in anti-diabetic pharmacotherapy (change in dosage or addition of new medication within 12 weeks of screening [with the exception of ± 10 units of insulin]) d. Anticipated need to change dose or type of medication during the treatment period of the Study [with the exception of ± 10 units of insulin] e. Current use of GLP-1 agonists	To define the exclusion criteria for each Group of patients and to make the eligibility criteria for the Group 3 patients consistent with those for the Group 1 index study patients

Protocol Section	Description of Change	Rationale
Protocol Synopsis: Study Population *Continued* 5.2 Exclusion Criteria *Continued*	**Is:** ***Continued*** **Exclusion Criteria for Group 3 (patients who did not participate in an index study)** 2. Severe hypertriglyceridemia other than due to familial chylomicronemia syndrome 3. Active pancreatitis within 4 weeks prior to screening 4. History within 6 months of screening of acute or unstable cardiac ischemia (myocardial infarction, acute coronary syndrome, new onset angina), stroke, transient ischemic attack or unstable congestive cardiac failure requiring a change in medication or major surgery within 3 months of screening 5. Any of the following laboratory values at Screening a. Hepatic: • Total bilirubin > upper limit of normal (ULN), unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL • ALT > 2.0 x ULN • AST > 2.0 x ULN b. Renal: • Persistently positive (2 out of 3 consecutive tests ≥ 1+) for protein on urine dipstick. In the event of a positive test eligibility may be confirmed by a quantitative total urine protein measurement of < 500 mg/24 hrs • Persistently positive (2 out of 3 consecutive tests ≥ trace positive) for blood on urine dipstick. In the event of a positive test eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field • Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault < 50 mL/min (MDRD or CKD-EPI formulas can be used instead of Cockcroft-Gault for estimation of GFR in patients with low body weight after discussion with Sponsor Medical Monitor) c. Cardiac Troponin I > ULN at Screening d. LDL-C > 130 mg/dL at Screening e. Any other laboratory abnormalities which, in the opinion of the Investigator or the Sponsor, would make the patient unsuitable for inclusion 6. Uncontrolled hypertension (BP > 160/100 mm Hg) 7. History of bleeding diathesis or coagulopathy or clinically-significant abnormality in coagulation parameters at Screening 8. History of heart failure with NYHA greater than Class II 9. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1 10. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B 11. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated 12. Treatment with another investigational drug, biological agent, or device within 1-month of screening, or 5 half-lives of investigational agent, whichever is longer 13. Unwilling to comply with lifestyle requirements (Section 6.3)	To define the exclusion criteria for each Group of patients and to make the eligibility criteria for the Group 3 patients consistent with those for the Group 1 index study patients *Continued*

Protocol Section	Description of Change	Rationale
Protocol Synopsis: Study Population *Continued* 5.2 Exclusion Criteria *Continued*	**Is:** ***Continued*** **Exclusion Criteria for Group 3 (patients who did not participate in an index study) *Continued*** 14. Use of any of the following: a. Statins, omega-3 fatty acids (prescription and OTC), or fibrates unless on a stable dose for at least 3 months prior to screening and dose and regimen expected to remain constant during the treatment period. Patients taking OTC omega-3 fatty acids should make every effort to remain on the same brand throughout the study b. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to screening c. Systemic corticosteroids or anabolic steroids within 6 weeks prior to screening unless approved by the Sponsor Medical Monitor d. Atypical antipsychotic medications (e.g., olanzapine and clozapine) unless on a stable dose for at least 3 months prior to screening and dose and regimen expected to remain stable throughout the study e. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to screening and dose and regimen expected to remain constant during the treatment period f. Glybera gene therapy within 2 years prior to screening g. Oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, and apixaban) unless on a stable dose for at least 4 weeks prior to screening and regular clinical monitoring is performed h. Tamoxifen, estrogens or progestins unless on a stable dose for at least 4 months prior to screening and dose and regimen expected to remain constant during the treatment period i. Plasma apheresis within 4 weeks prior to screening or planned during the study j. Prior exposure to ISIS 304801 k. Any other medication unless stable at least 4 weeks prior to screening (Occasional or intermittent use of over-the-counter medications will be allowed at Investigator's discretion) 15. Blood donation of 50 to 499 mL within 30 days of screening or of > 499 mL within 60 days of screening 16. Known hypersensitivity to any of the excipients of the Study Drug (ISIS 304801 or placebo) 17. Have any other conditions, which, in the opinion of the Investigator or the Sponsor would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the study	To define the exclusion criteria for each Group of patients and to make the eligibility criteria for the Group 3 patients consistent with those for the Group 1 index study patients *Continued*
Protocol Synopsis: Study Visit Schedule and Procedures 3.4 Overall Study Duration and Follow-up Appendix A	**Was:** The study for an individual patient will generally consist of the following periods: A qualification period of up to 2 weeks (unless approved by the Sponsor). Please refer to Section 4.1 and Appendix A. ○ A 52-week treatment period during which volanesorsen will be administered as a once weekly SC injection ○ A 13-week post-treatment evaluation period	To distinguish the Screening/ Qualification period for patients who participated in an index study from those who did not

Protocol Section	Description of Change	Rationale
Protocol Synopsis: Study Visit Schedule and Procedures *Continued* 3.4 Overall Study Duration and Follow-up *Continued* Appendix A *Continued*	**Is:** *Continued* The study for an individual patient will generally consist of the following periods: • Group 1 and 2 patients (participated in ISIS 304801-CS6 or ISIS 304801-CS16 index study): A qualification period of up to 2 weeks (unless approved by the Sponsor). Please refer to Section 4.1 and Appendix A. • Group 3 patients (did not participate in an index study): An up to 8-week screening and qualification period, including a diet stabilization period of at least 6 weeks (screening and diet stabilization period may be reduced, per Sponsor approval, if the patient is following a diet for optimal control of TGs and disease management prior to screening). Please refer to Section 6.1.2 and Appendix A. • All patients: o A 52-week treatment period during which volanesorsen will be administered as a once weekly SC injection o A 13-week post-treatment evaluation period	To distinguish the Screening/ Qualification period for patients who participated in an index study from those who did not *Continued*
4.1 Screening / Qualification	Group 3 (Screening and Qualification): At the time of consent, the patient will be considered enrolled into the study and will be assigned a unique screening number before any study procedures, including screening procedures, are performed. At the time of enrollment, patients will be assigned a unique patient identification number. This number will be used to identify the patient throughout the trial and must be used on all study documentation related to that patient. The screening number and patient identification number must remain constant throughout the entire trial. In the event the patient is re-consented and re-screened the patient must be given a new screening number. Screening numbers and patient identification numbers, once assigned, will not be re-used	To define the enrollment criteria for patients who did not participate in an index study
6.1.2 Screening and Qualification (Group 3)	Before any study-specific procedures or evaluations are initiated, patients must sign and date the informed consent form. An 8-week period, including a diet stabilization period of at least 6 weeks (screening and diet stabilization period may be reduced, per Sponsor approval, if the patient is following a diet for optimal control of TGs and disease management prior to screening) is given to perform the screening evaluations. The qualification assessments will be performed at Week -2 to -1, ideally after patient eligibility has been determined, and on Study Day 1. Abnormal screening results may be retested for review by the Study Medical Monitor for eligibility purposes	To define the Screening and Qualification procedures for patients who did not participate in an index study
8.6.3 Stopping Rules for Platelet Count Results	**Was:** If after the first dosing rechallenge the platelet count again falls below 75,000/mm^3, then dosing of the patient must be held until the platelet count again returns to at least 100,000/mm^3. The suitability of the patient for continued dosing and the need for any further modification to treatment schedule or dose (refer to Section 8.7) will be re-examined by the Investigator in consultation with the Study Medical Monitor based on (at least) the factors mentioned above. If after the second rechallenge the platelet count falls below 75,000/mm^3 and is subsequently confirmed (see Section 8.5), dosing with volanesorsen will be stopped permanently. The follow-up schedule for any events meeting this stopping criterion will be determined by the Investigator in consultation with the Study Medical Monitor.	Text was removed as a second Study Drug rechallenge will not be allowed following a platelet count decrease below 75,000/mm^3

<table>
<tr><th>Protocol Section</th><th>Description of Change</th><th>Rationale</th></tr>
<tr><td>8.6.3 Stopping Rules for Platelet Count Results Continued</td><td><u>Is:</u>
If after the first dosing rechallenge the platelet count again falls below 75,000/mm^3, then dosing of the patient with Study Drug will be stopped permanently.</td><td>Text was removed as a second Study Drug rechallenge will not be allowed following a platelet count decrease below 75,000/mm^3</td></tr>
<tr><td>8.6.3 Stopping Rules for Platelet Count Results
Table 2 Actions in Patients with Low Platelet Count</td><td>
<table>
<tr><th>Platelet Count on Rx</th><th>Drug Dose</th><th>Monitoring</th></tr>
<tr><td>Normal range, > 140K/mm^3</td><td>No action</td><td>Monitor every 2 weeks</td></tr>
<tr><td>100K-140K/mm^3</td><td>No action</td><td>Closer observation
Monitor every 1-week <u>until stable*</u></td></tr>
<tr><td>75K-100K/mm^3</td><td><u>Permanently</u> reduce dose frequency to 300mg every 2 weeks or reduce dose to 150 mg weekly</td><td>Closer observation
Monitor every 1-week</td></tr>
<tr><td>50K-75K/mm^3</td><td><u>If occurs while on dose of 300 mg every 2 weeks or 150 mg every week then permanently discontinue Study Drug, otherwise dose pause.</u>
<s>Dose pause</s>
When platelet count returns to > 100K/mm^3 restart dosing at dose frequency of 300 mg every 2 weeks or 150 mg weekly only if approved by Sponsor Medical Monitor</td><td>Closer observation
Monitor every 2-3 days until 2 successive values show improvement
Consider discontinuation of antiplatelet agents/NSAIDS/ anticoagulant medication</td></tr>
</table>
</td><td>To provide clarification to the platelet safety monitoring rules

Note: Changes are reflected as bold underlined text</td></tr>
</table>

<table>
<tr><th>Protocol Section</th><th>Description of Change</th><th>Rationale</th></tr>
<tr>
<td>8.6.3 Stopping Rules for Platelet Count Results
Table 2 Actions in Patients with Low Platelet Count
Continued</td>
<td>
<table>
<tr><th>Platelet Count on Rx</th><th>Drug Dose</th><th>Monitoring</th></tr>
<tr><td>25K-50K/mm^3</td><td>If occurs while on dose of 300 mg every 2 weeks or 150 mg every week then permanently discontinue Study Drug, otherwise dose pause.
When platelet count returns to > 100K/mm^3 restart dosing at dose frequency of 300 mg every 2 weeks or 150 mg weekly only if approved by Sponsor Medical Monitor</td><td>Closer observation
Monitor daily until 2 successive values show improvement then monitor every 2 3 days until platelet count stable
Discontinue antiplatelet agents/NSAIDS/anticoagulant medication while platelet count < 50K/mm^3 if possible</td></tr>
<tr><td>< 25K/mm^3</td><td>Permanently discontinue Study Drug</td><td>Closer observation:
Monitor daily until 2 successive values show improvement then monitor every 2-3 days until platelet count stable
Steroids recommended**
Consider need for hospitalization and referral to hematologist
Discontinue antiplatelet agents/NSAIDS/anticoagulant medication while platelet count < 50K/mm^3 if possible</td></tr>
</table>
* <u>At least 3 consecutive values measured weekly that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3</u>
** Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (note: may require continuation with oral steroids after methyl prednisolone)
</td>
<td>To provide clarification to the platelet safety monitoring rules

Note: Changes are reflected as bold underlined text
Continued</td>
</tr>
</table>

Protocol Section	Description of Change	Rationale
8.8.1 Follow-up Visits for Early Termination from Treatment Period	**Was:** Any patient who discontinues early from the Treatment Period should be strongly encouraged to attend applicable landmark visits at Weeks 2, 13, 25, 26, and 51, 52 (calculated based on the time elapsed since Day 1) to collect fasting lipid panels and conduct safety assessments in accordance with the schedule of procedures in Appendix A. Any patient who discontinues treatment after Week 44 should also be strongly encouraged to attend a final follow-up visit (Week 65 visit assessments) approximately 13 weeks after their last dose of Study Drug, in addition to the applicable landmark visits. **Is:** Any patient who discontinues early from the Treatment Period should be followed as per the platelet monitoring rules shown in Table 2 in Section 8.6.3 for the first 6 weeks after discontinuing Study Drug. Following this period, if the platelet count is stable (at least 3 consecutive values that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3), the next platelet count should be taken within at least 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug. Patients should also be strongly encouraged to attend applicable landmark visits at Weeks 12, 13, 25, 26, and 50, 52 (calculated based on the time elapsed since Day 1) to collect fasting lipid panels and conduct safety assessments in accordance with the schedule of procedures in Appendix A. Any patient who discontinues treatment after Week 44 should also be strongly encouraged to attend a final follow-up visit (Week 65 visit assessments) approximately 13 weeks after their last dose of Study Drug, in addition to the applicable landmark visits.	To provide guidance to the platelet safety monitoring rules for patients that discontinue early from the Treatment Period
8.8.2 Follow-up Visits for Early Termination from Post-Treatment Follow-up Period	**Was:** The patient who requests to withdraw from the study during the Post-Treatment Follow-up Period should be encouraged to undergo a final follow-up visit (Week 65, see Appendix A) prior to leaving the study. **Is:** The patient who requests to withdraw from the study during the Post-Treatment Follow-up Period should be encouraged to follow the platelet monitoring rules shown in Table 2 in Section 8.6.3 for the first 6 weeks after discontinuing Study Drug. Following this period, if the platelet count is stable (at least 3 consecutive values that are stable as determined by the Sponsor medical monitor and > 100,000/mm^3), the next platelet count should be taken within at least 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug. Patients should also be encouraged to undergo a final follow-up visit (Week 65, see Appendix A) prior to leaving the study.	To provide guidance to the platelet safety monitoring rules for patients that discontinue early from the Post-Treatment Follow-up Period

PROTOCOL SYNOPSIS

Protocol Title	An Open-Label Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Study Phase	3
Indication	Familial Chylomicronemia Syndrome
Study Objectives	To evaluate the safety and efficacy of dosing and extended dosing with volanesorsen (volanesorsen sodium 300 mg) in patients with FCS
Study Design	This is a multi-center open-label study of: Group 1: ISIS 304801-CS6 (index study) roll over FCS patients Group 2: ISIS 304801-CS16 (index study) roll over FCS patients Group 3: FCS patients who did not participate in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies All patients will receive volanesorsen 300 mg once per week for 52 weeks. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period. Following the Week 52 visit, patients will enter a 13-week post-treatment evaluation period.
Number of Patients	Up to approximately 70 patients dosed
Study Population	Inclusion Criteria: 1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law 2. Age ≥ 18 years at time of informed consent 3. Groups 1 and 2: Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement. Groups 2 and 3: Patients must also meet the following criteria in order to enter into the open-label study: a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L) b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) by documentation of the following: • Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1) c. Group 2: Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 index study Group 3: Fasting TG ≥ 750 mg/dL at Screening for this open-label study 4. Able and willing to participate in a 65-week study

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	Inclusion Criteria: *Continued* 5. Satisfy 1 of the following: a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved), abstinent*, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration b. Males: Surgically sterile, abstinent* or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration * Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception Exclusion Criteria for Group 1 (ISIS 304801-CS6) and Group 2 (ISIS 304801-CS16) Index Study Roll-over Patients 1. Have any new condition or worsening of existing condition which in the opinion of the Investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study 2. Unwilling to comply with lifestyle requirements for the duration of the study (Section 6.3) Exclusion Criteria for Group 3 (patients who did not participate in an index study) 1. Diabetes mellitus with any of the following: a. Newly diagnosed within 12 weeks of screening b. HbA1c ≥ 9.0% at Screening c. Recent change in anti-diabetic pharmacotherapy (change in dosage or addition of new medication within 12 weeks of screening [with the exception of ± 10 units of insulin]) d. Anticipated need to change dose or type of medication during the treatment period of the Study (with the exception of ± 10 units of insulin) e. Current use of GLP-1 agonists 2. Severe hypertriglyceridemia other than due to familial chylomicronemia syndrome 3. Active pancreatitis within 4 weeks prior to screening

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	Exclusion Criteria for Group 3 (patients who did not participate in an index study) *Continued* 4. History within 6 months of screening of acute or unstable cardiac ischemia (myocardial infarction, acute coronary syndrome, new onset angina), stroke, transient ischemic attack or unstable congestive cardiac failure requiring a change in medication or major surgery within 3 months of screening 5. Any of the following laboratory values at Screening a. Hepatic: • Total bilirubin > upper limit of normal (ULN), unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL • ALT > 2.0 x ULN • AST > 2.0 x ULN b. Renal: • Persistently positive (2 out of 3 consecutive tests ≥ 1+) for protein on urine dipstick. In the event of a positive test eligibility may be confirmed by a quantitative total urine protein measurement of < 500 mg/24 hrs • Persistently positive (2 out of 3 consecutive tests ≥ trace positive) for blood on urine dipstick. In the event of a positive test eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field • Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault < 50 mL/min (MDRD or CKD-EPI formulas can be used instead of Cockcroft-Gault for estimation of GFR in patients with low body weight after discussion with Sponsor Medical Monitor) c. Cardiac Troponin I > ULN at Screening d. LDL-C > 130 mg/dL at Screening e. Any other laboratory abnormalities which, in the opinion of the Investigator or the Sponsor, would make the patient unsuitable for inclusion 6. Uncontrolled hypertension (BP > 160/100 mm Hg) 7. History of bleeding diathesis or coagulopathy or clinically-significant abnormality in coagulation parameters at Screening 8. History of heart failure with NYHA greater than Class II 9. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1 10. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B 11. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated 12. Treatment with another investigational drug, biological agent, or device within 1-month of screening, or 5 half-lives of investigational agent, whichever is longer

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	Exclusion Criteria for Group 3 (patients who did not participate in an index study) *Continued* 13. Unwilling to comply with lifestyle requirements (Section 6.3) 14. Use of any of the following: a. Statins, omega-3 fatty acids (prescription and OTC), or fibrates unless on a stable dose for at least 3 months prior to screening and dose and regimen expected to remain constant during the treatment period. Patients taking OTC omega-3 fatty acids should make every effort to remain on the same brand throughout the study b. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to screening c. Systemic corticosteroids or anabolic steroids within 6 weeks prior to screening unless approved by the Sponsor Medical Monitor d. Atypical antipsychotic medications (e.g., olanzapine and clozapine) unless on a stable dose for at least 3 months prior to screening and dose and regimen expected to remain stable throughout the study e. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to screening and dose and regimen expected to remain constant during the treatment period f. Glybera gene therapy within 2 years prior to screening g. Oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, and apixaban) unless on a stable dose for at least 4 weeks prior to screening and regular clinical monitoring is performed h. Tamoxifen, estrogens or progestins unless on a stable dose for at least 4 months prior to screening and dose and regimen expected to remain constant during the treatment period i. Plasma apheresis within 4 weeks prior to screening or planned during the study j. Prior exposure to ISIS 304801 k. Any other medication unless stable at least 4 weeks prior to screening (Occasional or intermittent use of over-the-counter medications will be allowed at Investigator's discretion) 15. Blood donation of 50 to 499 mL within 30 days of screening or of > 499 mL within 60 days of screening 16. Known hypersensitivity to any of the excipients of the Study Drug (ISIS 304801 or placebo) 17. Have any other conditions, which, in the opinion of the Investigator or the Sponsor would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the study
Treatment Group	Volanesorsen 300 mg once per week
Study Drug Administration	Volanesorsen will be administered as subcutaneous (SC) injections.
Dose Adjustments	Dose adjustments, including dose interruptions and/or decreasing the dose frequency will be allowed for safety or tolerability after consultation with the Sponsor Medical Monitor.

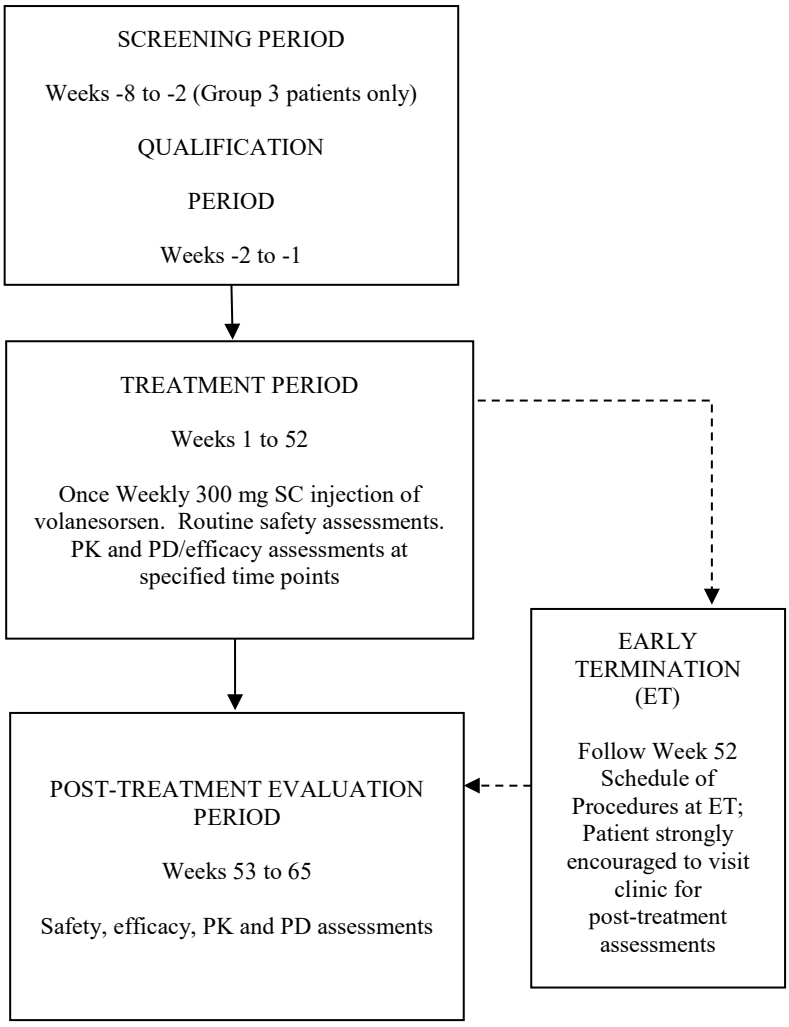
PROTOCOL SYNOPSIS *Continued*

Rationale for Dose and Schedule Selection	The dose of 300 mg once weekly was chosen for the double-blinded placebo-controlled Phase 3 index studies (ISIS 304801-CS6 and ISIS 304801-CS16) based on the pharmacodynamic and safety analysis of the Phase 2 studies (Section 2.4) which included a subset of patients with FCS. The same dose of 300 mg once weekly will be used in this open-label study of FCS patients.
Study Visit Schedule and Procedures	The study for an individual patient will generally consist of the following periods: • Group 1 and 2 patients (participated in ISIS 304801-CS6 or ISIS 304801-CS16 index study): A qualification period of up to 2 weeks (unless approved by the Sponsor). Please refer to Section 4.1 and Appendix A • Group 3 patients (did not participate in an index study): An up to 8-week screening and qualification period, including a diet stabilization period of at least 6 weeks (screening and diet stabilization period may be reduced, per Sponsor approval, if the patient is following a diet for optimal control of TGs and disease management prior to screening). Please refer to Section 6.1.2 and Appendix A • All patients: o A 52-week treatment period during which volanesorsen will be administered as a once weekly SC injection o A 13-week post-treatment evaluation period The patients, Investigators, study staff, and the Sponsor will remain blinded to lipid data through the last patient's Week 13 visit of the open-label study or until results from the database locks for the ISIS 304801-CS6 and ISIS 304801-CS16 index studies becomes available, whichever comes first. Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), adverse events (AE), concomitant medication/procedure information, lipid panel, volanesorsen plasma concentrations, immunogenicity (IM) testing, liver/spleen magnetic resonance imaging (MRI), ECGs, echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Dietary counseling will be repeated at intervals throughout the treatment and follow-up period and a daily food/drink diary will be completed for the week prior to each quarterly visit by each patient. Following the Week 52 visit, patients will enter the 13-week post-treatment evaluation period.

PROTOCOL SYNOPSIS *Continued*

Safety and Tolerability Evaluations	Overall safety and tolerability of volanesorsen will be assessed by determining the incidence and severity of adverse and serious adverse events (including independently adjudicated events of acute pancreatitis and MACE), withdrawals due to adverse events, and changes in laboratory and other safety parameters.
Planned Analyses	Safety Endpoints: • Adverse events including adjudicated events of acute pancreatitis and MACE • Vital signs and weight • Physical examinations • Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis) • Echocardiography • Electrocardiograms (ECGs) • Use of concomitant medications • MRIs Efficacy Endpoints: • Percent change and absolute change from baseline in fasting TG • Frequency and severity of patient reported abdominal pain during the treatment period • Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-high-density lipoprotein-cholesterol (non-HDL-C), apolipoprotein B [apoB], high-density lipoprotein-cholesterol (HDL-C), apolipoprotein A-1 [apoA-1], very-low-density lipoprotein-cholesterol (VLDL-C), and LDL-C • Percent change from baseline in fasting total apolipoprotein C-III (apoC-III) • Quality of Life questionnaires (EQ-5D, SF-36) • Adjudicated acute pancreatitis event rate • Other symptoms: eruptive xanthoma, lipemia retinalis
Pharmacokinetic Evaluations	Plasma samples will be taken from all patients for the measurement of volanesorsen as follows: trough levels (pre-dose) throughout treatment and post-treatment levels during the post-treatment follow-up period. In a subset of patients, more frequent assessment of plasma concentrations of volanesorsen will be performed to determine volanesorsen pharmacokinetic parameters. Plasma sample collection time points are detailed in Appendix A and Appendix C.
Statistical Considerations	No sample size calculations were performed as this is an open-label study.
Sponsor	Ionis Pharmaceuticals, Inc.
Collaborator	Akcea Therapeutics

STUDY DESIGN AND TREATMENT SCHEMA



STUDY GLOSSARY

Abbreviation/Acronym	Definition
ADA	anti-drug antibody
AE	adverse Event
ALP	alkaline Phosphatase
ALT	alanine Aminotransferase
ANA	antinuclear Antibody
apoA-1	apolipoprotein A-1
apoB	apolipoprotein B
apoC-III	apolipoprotein C-III
apoE	apolipoprotein E
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
CBC	complete blood count
C_{max}	maximum observed drug concentration
CRF	case report form
DNA	deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
ET	early termination
FAS	full analysis set
FCS	Familial Chylomicronemia Syndrome
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
GPIHBP1	Glycosylphosphatidylinositol-anchored HDL-binding Protein 1
HAPI	Heritability and Phenotype Intervention
HbA1c	Glycated Hemoglobin
HDL	High-Density Lipoprotein
HDL-C	High-Density Lipoprotein-Cholesterol
hsCRP	High-sensitivity C-reactive protein
ICH	International Conference on Harmonization
IDL	Intermediate density lipoprotein
IEC	Independent Ethics Committee
IM	immunogenicity
Index Studies	ISIS 304801-CS6 and ISIS 304801-CS16

INR	International Normalized Ratio
IRB	Institutional Review Board
IXRS	Interactive Voice/Web-Response System
LDL	Low-Density Lipoprotein
LDL-C	Low-Density Lipoprotein-Cholesterol
LMF1	Lipase Maturation Factor 1
LPL	Lipoprotein Lipase
MACE	Major Acute Cardiovascular Event
MOE	2′-*O*-(2-methoxyethyl)
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NCS	not clinically-significant
NOAEL	No-Observed-Adverse-Effect Level
non-HDL-C	Non-High-Density Lipoprotein-Cholesterol
OTC	over the counter
PFS	prefilled syringe
PD	pharmacodynamic
PK	pharmacokinetic
PPS	per protocol set
PT	prothrombin time
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SUSAR	suspected unexpected serious adverse reaction
T2DM	type 2 diabetes mellitus
T_{max}	time to maximal concentration
TG	triglycerides
Treatment-emergent	occurring after first dose of Study Drug
TRL	Triglyceride-Rich Lipoproteins
ULN	upper limit of normal
VLDL	Very-Low-Density Lipoprotein
VLDL-C	Very-Low-Density Lipoprotein-Cholesterol
VLDL-TG	Lipoprotein-Triglyceride
WMA	World Medical Association

1. OBJECTIVES

The objective of the study is to evaluate the safety and efficacy of dosing and extended dosing with volanesorsen in patients with familial chylomicronemia syndrome.

2. BACKGROUND AND RATIONALE

2.1 Overview of Disease

Familial Chylomicronemia Syndrome (FCS) is an inherited disease characterized by severe hypertriglyceridemia and chylomicronemia, and risk or history of pancreatitis. It is a rare autosomal recessive disease that can be diagnosed either in childhood or adulthood.

Fasting plasma triglyceride (TG) levels in FCS patients are typically 10-fold to 100-fold above normal (1,500 to 15,000 mg/dL), despite extreme dietary fat restriction (20 g or approximately 15-20% of daily calorie intake) (Brunzell 1999-2011). Patients with FCS often present in infancy or childhood with frequent and severe abdominal pain, repetitive colicky pain, repeated episodes of potentially fatal acute pancreatitis, and failure to thrive (Brunzell 1999-2011; Tremblay et al. 2011). Physical examination frequently reveals eruptive xanthomas, lipemia retinalis and hepatosplenomegaly, and plasma from patients appears lactescent, interfering with determination of other laboratory parameters (Tremblay et al. 2011).

Patients with fasting triglyceride levels > 10 mmol/L probably have a component of chylomicronemia. Clinical diagnosis would include evidence of clinical features of chylomicronemia syndrome and secondary causes such as uncontrolled type 1 or type 2 diabetes mellitus (T2DM), hypothyroidism, poor diet, alcohol use, nephrotic syndrome or use of associated medications should be ruled out. The diagnosis of FCS may be made more specifically by genotyping or confirmation of very low or absent lipoprotein lipase (LPL) enzyme activity in post heparin plasma (Brunzell 1999-2011).

Patients with FCS carry a heavy burden of medical complications, the most serious, as described above, being an extreme risk of recurrent and potentially fatal pancreatitis. Due to the recurrent episodes of acute pancreatitis, these patients may also develop chronic pancreatitis and signs of exocrine or endocrine pancreatic insufficiency, including diabetes mellitus (Gaudet et al. 2013). While the pathophysiology underlying chylomicron-related pancreatitis has not been completely elucidated, 1 hypothesis is that large chylomicrons lodged in pancreatic capillaries are exposed to pancreatic lipase, with the subsequent release of free fatty acids through the hydrolysis of chylomicron-associated TGs. High concentrations of free fatty acids are thought to damage pancreatic cells leading to emergent pancreatitis (Yang et al. 2009; Berglund et al. 2012).

The etiology of extreme hypertriglyceridemia in FCS is considered to be ineffective triglyceride clearance, due to an extremely low level of LPL activity. LPL normally functions to hydrolyze triglycerides (TG) in chylomicrons along the luminal surface of capillaries, mainly in heart, skeletal muscle, and adipose tissue, promoting triglyceride clearance from the circulation. LPL is regulated by a number of key genes, and loss-of-function mutations in one of these genes, or the LPL gene itself, results in FCS (Surendran et al. 2012). In addition to loss of function mutations, null mutations, and nonsense mutations in the LPL gene, other genes currently identified in FCS patients, and known to directly influence LPL activity include: apolipoprotein C-II (APOC2) a cofactor for LPL (Schuster et al. 2011); apolipoprotein A-V

(APOA5) an enhancer of LPL activity (Schaap et al. 2004); lipase maturation Factor 1 (LMF1), a transmembrane protein involved in LPL maturation (Doolittle et al. 2009); glycosylphosphatidylinositol-anchored HDL-binding protein 1 (GPIHBP1), a capillary endothelial cell protein that provides a platform for LPL-mediated processing of chylomicrons (Beigneux et al. 2007).

2.2 Therapeutic Rationale

Apolipoprotein C-III (ApoC-III), a key regulator of plasma triglyceride levels, is a 79 amino acid glycoprotein synthesized principally in the liver (Ooi et al. 2008; Figure 1). ApoC-III is a major regulator of lipoprotein metabolism and plays a pivotal role in regulating plasma TG levels (Chan et al. 2008). It is a component of triglyceride-rich lipoproteins (TRLs) and a potent inhibitor of LPL (Lemieux et al. 2003). At higher concentrations apoC-III also inhibits hepatic lipase activity (Kinnunen and Ehnolm 1976), an enzyme which plays an important role in the conversion of dense very-low-density lipoprotein (VLDL) to intermediate density lipoprotein (IDL) and to LDL (Mendivil et al. 2010), as well as in the remodeling of HDL (Brown et al. 2010). In addition, increased apoC-III content adversely affects apoE-mediated hepatic uptake of TG-rich remnants (Mann et al. 1997). Thus, elevated plasma apoC-III levels are associated with impaired hydrolysis and retarded clearance of TG-rich particles, resulting in the accumulation of lipoprotein-triglyceride (VLDL-TG) and chylomicrons in plasma and the development of hypertriglyceridemia (Ito et al. 1990).

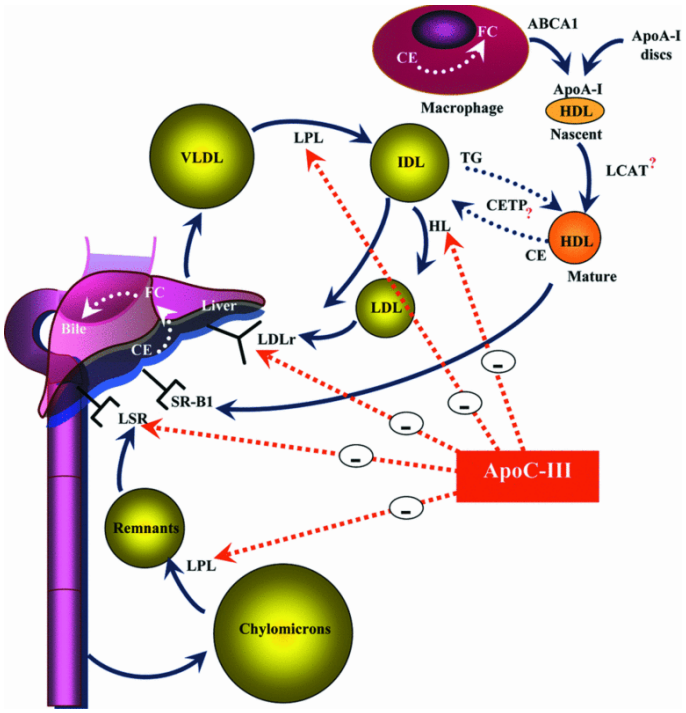


Figure 1 ApoC-III Regulates Lipoprotein Metabolism by Multiple Mechanisms

From Ooi et al. 2008; ABCA1 = ATP-binding cassette A1, apo = apolipoprotein, CE = cholesterol ester, CETP = cholesterol ester transfer protein, FC = free cholesterol, HDL = high-density lipoprotein, HL = hepatic lipase, IDL = intermediate-density lipoprotein, LCAT = lecithin cholesterol acyltransferase, LDL = low-density lipoprotein, LDLr = LDL receptor, LPL = lipoprotein lipase, LSR = lipolysis-stimulated receptor, SR-B1 = scavenger receptor B-1, TG = triglyceride, VLDL = very low-density lipoprotein.

Mechanistically, FCS is primarily a consequence of ineffective clearance of TRL. ApoC-III is a prominent component of TRL (e.g., VLDL and chylomicrons). In addition to its role in inhibiting LPL, apoC-III inhibits TRL remnant (TG-depleted remnant lipoprotein) uptake by hepatic lipoprotein receptors by steric inhibition of the interaction of apoE with these receptors.

Human genetic data have demonstrated positive phenotypic associations with loss (e.g., null or nonsense mutations) and negative effects with gain of function mutations (Atzmon et al. 2006; Pollin et al. 2008; Petersen et al. 2010). A novel nonsense mutation in the apoC-III gene was identified in the heritability and phenotype intervention (HAPI) heart study in Old Order Amish that results in lower plasma apoC-III and TG levels and lower LDL-C, increased HDL-C and reduced atherosclerosis (Pollin et al. 2008). In another study involving a group of 214 Ashkenazi Jews of advanced age (had passed or nearly reached 100 years of age), genotype analysis revealed a polymorphism in the apoC-III gene (APOC3-641CC genotype) with a clear pattern of age-dependent frequency that was associated with significantly lower levels of apoC-III protein, a favorable lipoprotein profile and increased longevity (Atzmon et al. 2006). In contrast to the Amish and Ashkenazi apoC-III polymorphisms associated with lower plasma TG, apoC-III polymorphisms associated with higher plasma TG have also been recently described (Petersen et al. 2010). In a cohort of lean (mean body mass index [BMI] = 24.7 ± 3.6 kg/m^2) Asian Indians, carriers of apoC-III variant alleles (C-482T, T-455C, or both) were noted to have significantly higher plasma apoC-III and TG levels, and decreased ability to clear postprandial plasma TG from the circulation. Taken together, the available data strongly support the development of a therapy that reduces plasma apoC-III levels in order to reduce the very high circulating triglyceride and chylomicron levels that are accompanied by increasing risk for acute pancreatitis.

Given the profound reductions in TGs observed with volanesorsen treatment in FCS patients who have no detectable LPL activity (See Section 2.3.4), and the mechanistic data available to date on apoC-III function, potential mechanisms that explain how apoC-III inhibition results in triglyceride reduction in FCS patients include: (1) enhancing the very small residual amounts of LPL activity that these patients may have, below the limit of detection of the assay in many cases (2) potentially enhanced activity of other lipases also involved in the metabolism and breakdown of TGs, such as hepatic lipase or endothelial lipase (Kinnunen and Ehnolm 1976), and (3) apoC-III interaction with Apolipoprotein E (apoE), an important factor in liver reuptake of lipid particles by blocking apoE-mediated uptake of lipid particles in the liver (Breyer et al. 1999), and therefore, reducing apoC-III might enhance apoE-mediated uptake of lipid particles. Volanesorsen-mediated reduction of apoC-III could be contributing to one or all of these mechanisms resulting in the observed potent and sustained reductions in TG.

Through a novel apoC-III lowering mechanism of action, volanesorsen may provide the potential to manage triglyceride levels in FCS patients.

2.3 Volanesorsen

2.3.1 Mechanism of Action

Volanesorsen is a second-generation antisense oligonucleotide (ASO) drug targeted to human apoC-III. It is complementary to a region within the 3′ untranslated region of the apoC-III messenger ribonucleic acid (mRNA) and binds to the mRNA by Watson and Crick base pairing.

The hybridization (binding) of volanesorsen to the cognate mRNA, results in the RNase H1-mediated degradation of the apoC-III mRNA, thus preventing production of the apoC-III protein. Maximal antisense-mediated reduction of target mRNA levels is typically greater than 90% of control levels in sensitive tissues (Crooke and Bennett 1996; Zhang et al. 2010). Furthermore, reduction in target mRNA levels using this approach correlates directly with a subsequent reduction in target protein levels.

2.3.2 Chemistry

Chemically, volanesorsen is a synthetic oligomer of 20 nucleotides (i.e., a 20-mer) that are connected sequentially by phosphorothioate linkages. The nucleotide sequence of volanesorsen (Figure 2) is complementary to a 20-nucleotide stretch within the 3′ untranslated region of the apoC-III mRNA transcript at base position 489-508. Structurally, the oligonucleotide has 3 regions. Two (2) of them, the 5 nucleotides at the 5′ end and the 5 nucleotides at the 3′ end, are composed of 2′-*O*-(2-methoxyethyl) (MOE)-modified ribonucleotides. These MOE-modified nucleotides confer (1) increased affinity to the target mRNA (Altmann et al. 1996; McKay et al. 1999), (2) increased resistance to exonucleases and endonucleases (thereby increasing stability in tissue) (Geary et al. 2003), and (3) amelioration of some of the high dose toxicities thereby resulting in an improved safety profile compared to first generation antisense drugs containing phosphorothioate modified oligodeoxynucleotides (DNA) (Henry et al. 2000). The third region, the central portion of the oligonucleotide, is composed of 10 oligodeoxynucleotides. This chimeric design is called a MOE-Gapmer, and volanesorsen employs this chimeric structure to enable use of the RNase H1-mechanism for antisense activity. This is because while the 2′-MOE modification confers increased stability and affinity, it does not support RNase H1 catalysis of RNA hybridized to 2′-MOE-modified nucleotides (McKay et al. 1999). This is caused by conformational changes induced in the heteroduplex by 2′-alkoxy:RNA hybrids that are not recognized by RNase H1 enzymes (Inoue et al. 1987; Monia et al. 1993). By limiting the 2′-MOE modification to nucleotides flanking the phosphorothioate oligodeoxynucleotide core, the beneficial attributes of the 2′-MOE chemistry are preserved while also retaining RNase H1 recognition.

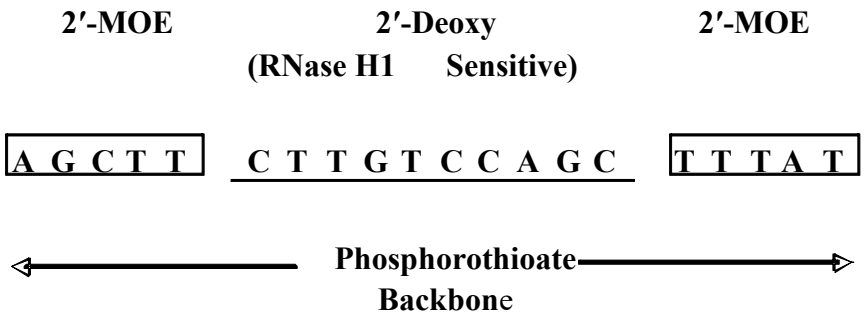


Figure 2 Design of Chimeric 2′-MOE Phosphorothioate Oligonucleotides (MOE-Gapmer). The sequence of volanesorsen is shown

2.3.3 Preclinical Experience

Inhibition of apoC-III using volanesorsen has been shown to potently reduce hepatic apoC-III mRNA as well as plasma apoC-III protein and TG in a dose- and time-dependent fashion in several species, including human apoC-III transgenic mice, and other rodent and monkey models. Treatment with volanesorsen also resulted in reduced VLDL and chylomicron TG and reduced postprandial TG in hypertriglyceridemic monkeys (Graham et al. 2013).

The pharmacokinetics (PK) and toxicity of volanesorsen have been assessed in mice, rats, and cynomolgus monkeys. General toxicity studies with volanesorsen for up to 39 weeks of treatment followed by up to a 20-week recovery period are complete. The preclinical toxicology program for volanesorsen consists of single dose safety pharmacology studies in the monkey (cardiovascular) and mouse (neurobehavioral and pulmonary assessment studies), *in vitro* and *in vivo* genetic toxicity assessment, repeat dose fertility and/or developmental reproductive toxicology studies in the mouse and rabbit and evaluation in the *in vitro* human Ether-á-go-go-related gene (hERG) assay.

Volanesorsen treatment-related findings in mice and monkeys were generally consistent with those expected for the 2′-MOE-class of ASOs. Treatment-related findings included effects consistent with drug accumulation in tissues in rodents and monkeys, species-dependent proinflammatory response in rodents and monkeys and complement activation and reductions in platelet counts in the monkey. In the mouse and monkey general toxicity studies, reduction of hepatic apoC-III mRNA (> 75%) was not associated with any findings that could be considered related to the pharmacologic inhibition of apoC-III for up to 39 weeks of treatment.

The long-term, chronic toxicology studies in rodents with volanesorsen produced a significant proinflammatory response that led to subsequent effects on the heart at high doses. The rodent species are most sensitive to the proinflammatory effects of antisense molecules. Importantly, these effects on the heart were not observed in the monkey chronic toxicity studies even at the highest doses tested where drug exposure was higher than that in rodents.

Because these changes were not observed in monkeys, the findings in the heart are considered to be rodent-specific and not relevant to humans. Nevertheless, such effects will be monitored by measurement of echocardiograms that will be included in this clinical study.

Volanesorsen caused no untoward effects in safety pharmacology studies (*in vitro* and *in vivo*) and was non-genotoxic (*in vitro* and *in vivo*). Volanesorsen had no effects on fertility or embryo/fetal development in the mouse or rabbit reproductive toxicity studies. In these studies, volanesorsen was detected in placental tissue but not in fetal tissue indicating that little, if any, drug was able to cross the placenta to reach the fetus. Reduction of apoC-III mRNA (64% in males and 47% in females) also did not affect fertility or cause untoward effects on embryo/fetal development in mice.

Detailed information concerning the preclinical studies conducted with volanesorsen can be found in the volanesorsen Investigator's Brochure.

2.3.4 Clinical Experience

Detailed information concerning the clinical studies conducted with volanesorsen can be found in the volanesorsen Investigator's Brochure. A summary is included below.

Volanesorsen has been evaluated in one Phase 1 study and two Phase 2 studies, all double blinded and placebo controlled. The total exposures comprise 99 patients and healthy volunteers administered volanesorsen from 50 to 400 mg subcutaneously up to 3 months (compared to 37 administered placebo).

All clinical trials of volanesorsen have shown large and clinically meaningful reductions in fasting plasma apoC-III and TG (~80% and 70%, respectively, mean reduction from baseline with 300 mg dose) with a very high degree of consistency of response between the different patient groups. This includes healthy volunteers, patients with moderate to severe hypertriglyceridemia not on background TG-lowering therapy, patients with moderate to severe hypertriglyceridemia on a background stable fibrate therapy (Gaudet et al. 2015), patients with FCS, and patients with T2DM.

In a Phase 2 study, 3 patients with FCS were treated with 300 mg/wk volanesorsen in an open-label fashion. These patients had a mean baseline fasting TG level of 1,844 mg/dL and all 3 patients achieved TG levels below or close to 500 mg/dL during the dosing period out to Day 92 (Figure 3). Two (2) of the FCS patients had an absolute reduction in fasting TG in excess of 1,500 mg/dL (Gaudet et al. 2014).

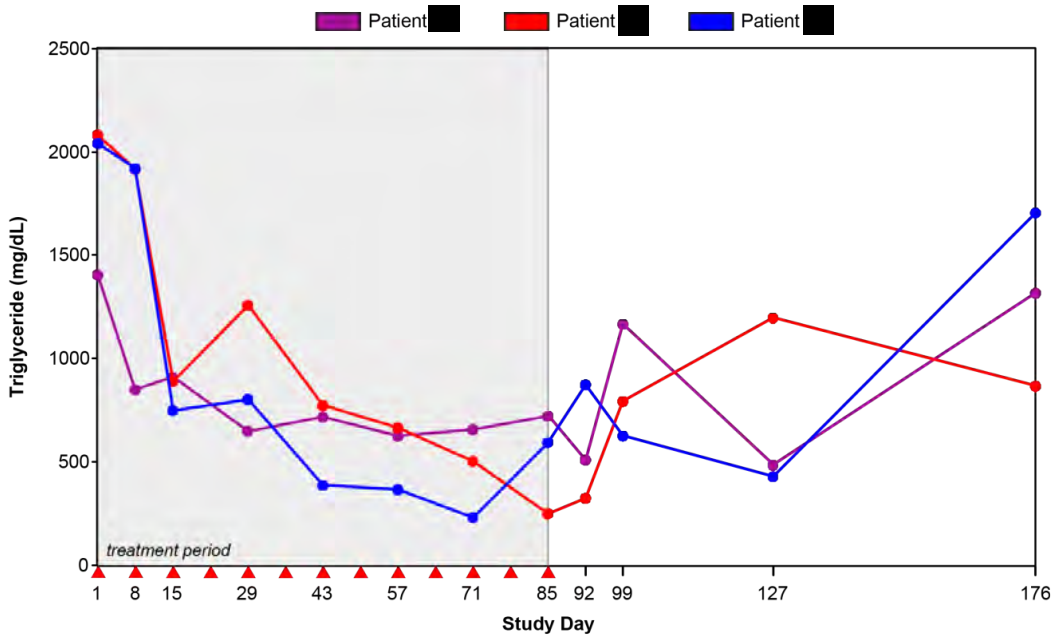


Figure 3 Fasting Triglycerides in Patients with FCS Treated with Volanesorsen

In clinical studies conducted to date volanesorsen has been well-tolerated and has shown a favorable safety profile. There has been no clinical or laboratory evidence of drug-drug interactions.

In the completed studies there have been no volanesorsen associated laboratory abnormalities suggestive of an effect on the renal (serum creatinine, proteinuria) or hepatic systems (alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin). In Phase 2 studies, there was a mild decrease of platelet count associated with volanesorsen administration that recovered in the post-treatment period and was not associated with platelet-related adverse events (AEs). In the blinded ongoing clinical trials of ISIS 304801, 2 patients of 142 dosed (as of February 29, 2016) had a decrease in platelet count to less than 50,000/mm^3 in the absence of major bleeding or clinically-relevant non-major bleeding and had Study Drug paused as per the monitoring and stopping rules for platelet counts (Section 8.6.3). Platelet counts recovered following suspension of dosing.

The most frequently observed AEs with volanesorsen were local reactions at the injection site. Local cutaneous reactions at the injection site defined as those events presenting as either pain, tenderness, erythema, pruritus or swelling occurring on the day of injection and persisting for at least 2 days were infrequent (~15% of injections), were almost always mild, resolved spontaneously, were non-progressive, and were not associated with systemic sequelae.

2.4 Rationale for Dose and Schedule of Administration

The dose and schedule selected for this study is 300 mg per week for 52 weeks. The dose of 300 mg per week is supported by both the cumulative nonclinical data available to date and the Phase 2 clinical data. In nonclinical studies, volanesorsen treatment-related effects in rodents and monkeys were consistent with drug accumulation in tissues and also include species-specific proinflammatory responses. In the monkey, the No-Observed-Adverse-Effect Level (NOAEL) was defined by the cumulative clinical pathology results and histopathology data which provide an adequate clinical margin. No nonclinical findings were considered to be related to the pharmacologic inhibition of apoC-III.

The safety data to date suggest that volanesorsen has been well-tolerated at dose levels up to 300 mg in patients with high triglycerides (including type 2 diabetes patients and administration in combination with fibrates and statins) with the most common AEs being local to the injection site and predominantly mild. A pooled analysis of safety for the Phase 2 studies did not demonstrate any clear difference in safety or tolerability between the different doses tested (100 mg, 200 mg, and 300 mg per week for 13 weeks).

Analysis of the cohorts in which volanesorsen was studied at different doses demonstrates dose-dependent pharmacology with respect to pharmacodynamic (PD) effect on the target, apoC-III, with a clear difference in the TG-lowering effect between the different doses in the 100 mg to 300 mg dose range as compared to placebo.

In addition to the nonclinical and clinical experience of volanesorsen, the dose and schedule of administration is supported by the preclinical and clinical safety experience of several other 2′-MOE-modified ASOs that have been safely administered intravenously and subcutaneously in multiple clinical studies at doses up to 1000 mg and for treatment durations that exceed 24 months (Santos et al. 2015).

3. EXPERIMENTAL PLAN

3.1 Study Design

This is an open-label study of:

Group 1: ISIS 304801-CS6 (index study) roll over FCS patients

Group 2: ISIS 304801-CS16 (index study) roll over FCS patients

Group 3: FCS patients who did not participate in the ISIS 304801-CS6 or ISIS 304801-CS16 index studies

Up to approximately 70 patients will receive 300 mg once weekly volanesorsen for 52 weeks.

Following the Week 52 visit, patients enter a 13-week post-treatment evaluation period.

3.2 Number of Study Centers

This study will be conducted at multiple centers worldwide.

3.3 Number of Patients

Up to approximately 70 patients will be dosed.

3.4 Overall Study Duration and Follow-up

The Study will consist of the following periods:

3.4.1 Group 1 and 2 Patients (participated in ISIS 304801-CS6 or ISIS 304801–CS16 index study): Qualification

A period of up to 2 weeks (unless approved by the Sponsor) is given to complete qualification assessments outlined in the Schedule of Procedures. Please refer to Section 4.1 and Appendix A.

3.4.2 Group 3 Patients (did not participate in an index study): Screening/Qualification

An up to 8-week screening and qualification period, including a diet stabilization period of at least 6 weeks (screening and diet stabilization period may be reduced, per Sponsor approval, if the patient is following a diet for optimal control of TGs and disease management prior to screening. Please refer to Section 6.1.2 and Appendix A.

3.4.3 Treatment

The treatment period is 52 weeks. Eligible patients will report to the Study Center for assessments at specified intervals throughout the 52-week treatment period as detailed in the Schedule of Procedures (Appendix A). During the treatment period, volanesorsen is administered by SC injection once weekly.

3.4.4 Post-Treatment

The post-treatment evaluation period is 13 weeks and consists of 2 Study Center visits on Weeks 58 and 65.

3.5 End-of-Study

The End-of-Study is last patient, last visit.

3.6 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will review (as needed) safety, tolerability and efficacy data collected on volanesorsen during this study. Based on its ongoing assessment of the safety and tolerability of volanesorsen, the DSMB will provide recommendations to the Sponsor for modifying, stopping or continuing the study as planned. Details on the safety assessments, frequency of review and meeting schedules are outlined in the DSMB Charter and/or the statistical analysis plan (SAP).

4. PATIENT ENROLLMENT

4.1 Screening/Qualification

Before patients may be enrolled into the study, the Sponsor requires a copy of the Study Center's written independent ethics committee/institutional review board (IEC/IRB) approval of the protocol, informed consent form, and all other patient information.

Patients or their legally acceptable representatives must sign the consent form before any study-specific procedures or evaluations related to this open-label study are performed.

Groups 1 and 2 (Qualification): During the qualification period, the eligibility of the patient to enroll in the open-label study will be determined. Final assessments from the ISIS 304801-CS6 or ISIS 304801-CS16 studies may be used for qualification. A period of up to 2 weeks after completion of the ISIS 304801-CS6 or ISIS 304801-CS16 index studies (unless approved by the Sponsor) is given to complete qualification. Qualified patients will retain the unique patient identification number that was assigned to them during the ISIS 304801-CS6 or ISIS 304801-CS16 index studies. The patient identification number will be used to identify the patient throughout the extension trial and must be used on all study documentation related to that patient. The patient identification number must remain constant throughout the extension trial.

Group 3 (Screening and Qualification): At the time of consent, the patient will be considered enrolled into the study and will be assigned a unique screening number before any study procedures, including screening procedures, are performed. At the time of enrollment, patients will be assigned a unique patient identification number. This number will be used to identify the patient throughout the trial and must be used on all study documentation related to that patient. The screening number and patient identification number must remain constant throughout the entire trial. In the event the patient is re-consented and re-screened the patient must be given a new screening number. Screening numbers and patient identification numbers, once assigned, will not be re-used.

4.2 Enrollment

Patients will be enrolled into the treatment phase of the study after all Screening (Group3) and qualification assessments have been completed and after the Investigator has verified that they are eligible per criteria in Sections 5.1 and 5.2. No patient may begin treatment prior to enrollment.

Eligible patients will be enrolled using an Interactive Voice/Web-Response System (IXRS).

5. PATIENT ELIGIBILITY

To be eligible to participate in this study candidates must meet the following eligibility criteria within 2 weeks of Study Day 1, or at the time point specified in the individual eligibility criterion listed.

5.1 Inclusion Criteria

1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law

2. Age ≥ 18 years at time of informed consent

3. Groups 1 and 2: Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement.

   Groups 2 and 3: Patients must also meet the following criteria in order to enter into the open-label Study:

   a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L)

   b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) by documentation of the following:

      - Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1)

   c. Group 2: Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 index study
      Group 3: Fasting TG ≥ 750 mg/dL at Screening for this open-label study

4. Able and willing to participate in a 65-week study

5. Satisfy 1 of the following:

   a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved), abstinent*, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration.

b. Males: Surgically sterile, abstinent* or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration.

* Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception

5.2 Exclusion Criteria for Group 1 (ISIS 304801-CS6) and Group 2 (ISIS 304801-CS16) Index Study Roll-over Patients

1. Have any new condition or worsening of existing condition which in the opinion of the Investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study.

2. Unwilling to comply with lifestyle requirements for the duration of the study (Section 6.3).

Exclusion Criteria for Group 3 (patients who did not participate in an index study)

1. Diabetes mellitus with any of the following:

   a. Newly diagnosed within 12 weeks of screening

   b. HbA1c $\geq$ 9.0% at Screening

   c. Recent change in anti-diabetic pharmacotherapy (change in dosage or addition of new medication within 12 weeks of screening [with the exception of $\pm$ 10 units of insulin])

   d. Anticipated need to change dose or type of medication during the treatment period of the Study (with the exception of $\pm$ 10 units of insulin)

   e. Current use of GLP-1 agonists

2. Severe hypertriglyceridemia other than due to familial chylomicronemia syndrome

3. Active pancreatitis within 4 weeks prior to screening

4. History within 6 months of screening of acute or unstable cardiac ischemia (myocardial infarction, acute coronary syndrome, new onset angina), stroke, transient ischemic attack or unstable congestive cardiac failure requiring a change in medication or major surgery within 3 months of screening

5. Any of the following laboratory values at Screening

   a. Hepatic:

      - Total bilirubin > upper limit of normal (ULN), unless prior diagnosis and documentation of Gilbert's syndrome in which case total bilirubin must be ≤ 3 mg/dL
      - ALT > 2.0 x ULN
      - AST > 2.0 x ULN

   b. Renal:

      - Persistently positive (2 out of 3 consecutive tests ≥ 1+) for protein on urine dipstick. In the event of a positive test eligibility may be confirmed by a quantitative total urine protein measurement of < 500 mg/24 hrs
      - Persistently positive (2 out of 3 consecutive tests ≥ trace positive) for blood on urine dipstick. In the event of a positive test eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field
      - Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault < 50 mL/min (MDRD or CKD-EPI formulas can be used instead of Cockcroft-Gault for estimation of GFR in patients with low body weight after discussion with Sponsor Medical Monitor)

   c. Cardiac Troponin I > ULN at Screening

   d. LDL-C > 130 mg/dL at Screening

   e. Any other laboratory abnormalities which, in the opinion of the Investigator or the Sponsor, would make the patient unsuitable for inclusion

6. Uncontrolled hypertension (BP > 160/100 mm Hg)

7. History of bleeding diathesis or coagulopathy or clinically-significant abnormality in coagulation parameters at Screening

8. History of heart failure with NYHA greater than Class II

9. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1

10. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B

11. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated

12. Treatment with another investigational drug, biological agent, or device within 1-month of screening, or 5 half-lives of investigational agent, whichever is longer
13. Unwilling to comply with lifestyle requirements (Section 6.3)
14. Use of any of the following:
    a. Statins, omega-3 fatty acids (prescription and OTC), or fibrates unless on a stable dose for at least 3 months prior to screening and dose and regimen expected to remain constant during the treatment period. Patients taking OTC omega-3 fatty acids should make every effort to remain on the same brand throughout the study
    b. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to screening
    c. Systemic corticosteroids or anabolic steroids within 6 weeks prior to screening unless approved by the Sponsor Medical Monitor
    d. Atypical antipsychotic medications (e.g., olanzapine and clozapine) unless on a stable dose for at least 3 months prior to screening and dose and regimen expected to remain stable throughout the study
    e. Antihypertensive medication unless on a stable dose for at least 4 weeks prior to screening and dose and regimen expected to remain constant during the treatment period
    f. Glybera gene therapy within 2 years prior to screening
    g. Oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, and apixaban) unless on a stable dose for at least 4 weeks prior to screening and regular clinical monitoring is performed
    h. Tamoxifen, estrogens or progestins unless on a stable dose for at least 4 months prior to screening and dose and regimen expected to remain constant during the treatment period
    i. Plasma apheresis within 4 weeks prior to screening or planned during the study
    j. Prior exposure to ISIS 304801
    k. Any other medication unless stable at least 4 weeks prior to screening (Occasional or intermittent use of over-the-counter medications will be allowed at Investigator's discretion)
15. Blood donation of 50 to 499 mL within 30 days of screening or of > 499 mL within 60 days of screening
16. Known hypersensitivity to any of the excipients of the Study Drug (ISIS 304801 or placebo)
17. Have any other conditions, which, in the opinion of the Investigator or the Sponsor would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the study

6. STUDY PROCEDURES

6.1 Study Schedule

All required study procedures are outlined in Appendices A, B, C, and D.

6.1.1 Qualification (Groups 1 and 2)

Please refer to Section 4.1 and Appendix A.

6.1.2 Screening and Qualification (Group 3)

Before any study-specific procedures or evaluations are initiated, patients must sign and date the informed consent form. An 8-week period, including a diet stabilization period of at least 6 weeks (screening and diet stabilization period may be reduced, per Sponsor approval, if the patient is following a diet for optimal control of TGs and disease management prior to screening) is given to perform the screening evaluations. The qualification assessments will be performed at Week -2 to -1, ideally after patient eligibility has been determined, and on Study Day 1. Abnormal screening results may be retested for review by the Study Medical Monitor for eligibility purposes

6.1.3 Treatment Period

The patients, Investigators, study staff, and the Sponsor will remain blinded to lipid data through the last patient's Week 13 visit of the open-label study or until results from the database locks for the ISIS 304801-CS6 and ISIS 304801-CS16 index studies become available, whichever comes first.

During the treatment period, patients will report to the study center for clinic visits a minimum of 5 times during Weeks 1-52 (see Schedule of Procedures in Appendix A). Study Drug will be administered once weekly (Section 8.1). Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), AEs, concomitant medication/procedure information, lipid panel, volanesorsen plasma concentrations, immunogenicity (IM) testing, liver/spleen MRI, ECGs, echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Adverse events at the injection site should be collected as adverse events. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period and all patients will complete a daily food diary for one week prior to their quarterly visit. All blood and urine samples should be collected prior to volanesorsen administration. Blood sampling at Weeks 2.5, 4, 6, 8, 10, 12, 15, 17, 19, 21, 23, 25, 28, 30, 32, 34, 36, 40, 42, 44, 46, 48, and 50 may be conducted by a home healthcare nurse. Approval for study procedures to be conducted by a home healthcare nurse on other outpatient visit days will require prior approval by the Sponsor. Patients must be fasted prior to drawing all blood samples and samples drawn locally should also be sent to the central laboratory for analysis whenever possible. Every effort should be made to ensure the previous week's dose is given 7 days prior to a scheduled clinic visit. Dosing instructions and training will be provided to the patient where applicable.

All reasonable attempts should be made to ensure compliance with the visit schedule as outlined in Appendix A. However, in the event that a visit does not occur or is delayed, all subsequent visits should be calculated based on the time elapsed since Day 1 rather than from the date of the previous visit.

6.1.4 Pharmacokinetic (PK) Subgroup

A subgroup of patients will participate in an extended PK collection. Patients in this subgroup will have more frequent PK sampling over a 24-hour period following the first dose on Study Day 1 in order to evaluate the plasma PK parameters of volanesorsen. Patients in this subgroup will have an additional visit to the clinic, or by a home healthcare nurse, on Day 2 to collect a 24-hour post-dose blood draw after dosing on Day 1. The detailed PK sampling schedules are outlined in Appendix C.

Participation in the PK subgroup is optional for sites and patients, and consent may be withdrawn for the subgroup-specific procedures (e.g., multiple blood draws for PK) without being withdrawn from the study. If a patient withdraws consent from the subgroup procedures, he/she should remain on study and continue to follow all the non-subgroup assessments and procedures as outlined in Appendix A.

6.1.5 Post-Treatment Period

After completion of the Week 52 visit assessments, patients will enter the 13-week post-treatment evaluation period. This period consists of 4 Study Center visits on Weeks 54, 56, and 58 (which may be conducted by a home healthcare nurse), and Week 65 as outlined in the Schedule of Procedures in Appendix A.

6.2 Additional Study Assessments

6.2.1 Laboratory Assessments

Laboratory analyte samples will be collected throughout the study. A list of these analytes is contained in Appendix B.

Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1-week and determined not to have met a stopping rule before dosing can continue.

If there is no reportable platelet count within 14 days of the last platelet count, the Investigator will contact the patient to hold dosing until a new platelet count is obtained and reviewed.

All platelet count results will be promptly reviewed by the Investigator to ensure that the count has not met the stopping rule and to determine whether the rate of decline is suggestive that the patient could be approaching the dose pause rule of 75,000/mm^3.

Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor.

6.2.2 Physical Exams and Vital Signs

Physical exams and vital signs will be performed as indicated in the Schedule of Procedures (Appendix A). Vital signs should include weight, blood pressure, pulse rate, respiratory rate and body temperature. Blood pressure and pulse rate will be recorded after the patient has been in a sitting position for at least 5 minutes. Semi-supine systolic and diastolic blood pressure should

always be measured on the same arm (preferentially on the left arm). Height will be measured at the Day 1 visit.

6.2.2.1 Eruptive Xanthoma

At each visit, patients will be asked whether they have had any episodes of eruptive xanthoma since their last visit and the number/duration of the events will be recorded. Physical exams should also include skin examination for presence/resolution of eruptive xanthomas. If a patient experiences an episode of eruptive xanthoma during the study, photos of the area should be taken, if possible.

6.2.2.2 Lipemia Retinalis

If possible, lipemia retinalis will be assessed by fundus photography prior to administration of the first dose of Study Drug (for ISIS 304801-CS16 rollover patients) and repeated at Week 52. Images will be evaluated by an independent assessor, blinded to the patient's treatment assignment.

6.2.3 Echocardiography

Echocardiography for assessment of left and right ventricular function and mitral and aortic valve function will be conducted at Week 26 and Week 52 in all patients. For the purpose of assessment of treatment-emergent changes, all echocardiograms will be evaluated on an ongoing basis by an independent central reader. Results will be provided to the DSMB for their review.

6.2.4 ECG

The ECG will be recorded after the patient has been resting in a supine position for at least 5 minutes. ECGs will be performed in triplicate at Week 13, Week 26, Week 38, Week 52, and Week 65.

6.2.5 MRI

MRI of the liver and spleen will be conducted at Week 52 for all patients for whom MRI is not contraindicated, e.g., patients having metal implants.

MRIs will be conducted using standardized procedures and settings. MRIs will be read by an independent central reader to assess liver fat and liver and spleen size**.**

6.2.6 Quality of Life Assessments

All patients will complete Quality of Life Questionnaires (EQ-5D and SF-36) at Week 1, Week 13, Week 26, Week 52, and Week 65.

6.2.7 Disease Symptom Diary

All patients will complete a symptom questionnaire once a week starting at the beginning of the qualification period and continuing to the end of the post-treatment follow-up period.

6.2.8 Diet Monitoring

The diets of patients enrolled in the study will be monitored as follows:

1. All patients will be required to maintain a 7-day food diary prior to Week 1, Week 13, Week 26, Week 52, and Week 65.

2. Patients will receive diet/alcohol counseling by qualified study personnel at clinic visits throughout the course of the study. Qualified study personnel will telephone the patient to provide diet/alcohol counseling for visits that are conducted by a clinical service.

3. In addition to the 7-day food diary and the diet /alcohol counseling during clinic visits, telephone calls from a dietitian or qualified study personnel to assess as to how each patient is maintaining their diet will be conducted randomly during the treatment and post treatment follow-up periods.

6.2.9 Family History

Family history of hypertriglyceridemia and pancreatitis will be collected for each patient.

6.3 Restriction on the Lifestyle of Patients

6.3.1 Contraception Requirements

All male patients and women of childbearing potential must refrain from sperm/egg donation and either be abstinent* or, if engaged in sexual relations of child-bearing potential, practice effective contraception from the time of signing the informed consent form until at least 13 weeks after their last dose of study treatment.

Male patients must also encourage their female partner to use effective contraception from the time of signing the informed consent until 13 weeks after the subject's last dose of study treatment.

For the purposes of this Study, women of childbearing potential are defined as any female who has experienced menarche, and who does not meet 1 of the following conditions:

- Postmenopausal: 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved

- 6 weeks after surgical bilateral oophorectomy with or without hysterectomy

- Post hysterectomy

For the purposes of the study, effective contraception is defined as follows:

For male patients:

- Effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the use of condoms together with spermicidal foam/gel/film/ cream/suppository. Male patients must also encourage their female partner to use

effective contraception from the time of signing the informed consent until 3 months after the patient's last dose of study treatment. Effective contraceptive for the female partner includes: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or barrier methods (female condom*, diaphragm, sponge, cervical cap) together with spermicidal foam/gel/film/cream/suppository. Male patients with partners that are pregnant must use condoms to ensure that the fetus is not exposed to the Study Drug.

For female patients:

- Using 1 or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or any 2 barrier methods (a combination of male or female condom* with diaphragm, sponge, or cervical cap) together with spermicidal foam/gel/film/cream/suppository.

*Note: A female condom and a male condom should not be used together as friction between the two can result in either product failing.

* Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception

6.3.2 Other Requirements

All patients will be required to fast for at least 10 hours and preferably not more than 12 hours before visits requiring fasted blood sampling.

All patients will be encouraged to follow a diet comprising ≤ 20 g fat per day during the study.

Alcohol should not be consumed during the study.

All patients will be given an instruction card that must be presented to the treating physician if a suspected case of pancreatitis occurs. The card will explain that the patient is in a clinical trial and that serum lipase and/or amylase measures should be done in order to adjudicate the event, based on Atlanta Classification (Banks et al. 2013). If serum or amylase activity is less than 3 x upper limit of normal (ULN), imaging, preferably contrast-enhanced computed tomography, should be considered to confirm the diagnosis of acute pancreatitis per the Atlanta Criteria.

7. STUDY DRUG

7.1 Volanesorsen Description

Volanesorsen drug product (ISIS 304801) characteristics are listed in Table 1.

Volanesorsen (ISIS 304801) is contained in glass prefilled syringes (PFS). Volanesorsen and its storage and preparation instructions will be provided by the Sponsor or designee. Volanesorsen must be stored securely at 2° to 8° C and be protected from light.

Table 1 Volanesorsen (ISIS 304801) Characteristics

Strength	200 mg/mL
Volume/Formulation	1.5 mL solution per PFS
Dose	300 mg once weekly
Route of Administration	SC

7.2 Packaging and Labeling

The Sponsor will provide the Investigator with packaged volanesorsen labeled (ISIS 304801) in accordance with specific country regulatory requirements.

7.3 Study Drug Accountability

The study staff is required to document the receipt, dispensing, and return/destruction of volanesorsen provided by the Sponsor. The Study Center must return all unused volanesorsen to the Sponsor or designee. All used syringes must be disposed of as per the site's hazardous waste destruction policy.

8. TREATMENT OF PATIENTS

8.1 Volanesorsen Administration

For each individual patient, volanesorsen will be administered subcutaneously as a single 1.5 mL 300 mg injection once weekly for Weeks 1-52. Patients entering this ISIS 304801-CS7 study on a reduced dose or dose frequency of Study Drug (volanesorsen), for safety or tolerability reasons in their index study (ISIS 304801-CS6 or ISIS 304801-CS16), will receive a reduced dose or dose frequency of volanesorsen for continued safety or tolerability as outlined in Sections 8.5 and 8.6. Patients entering this CS7 study having dose or dose frequency reduced in the CS16 index study after 13 weeks of treatment, as outlined in CS16 Amendment 4 Section 8.7, can receive the 300 mg once weekly dose of volanesorsen.

Patients should receive 1 dose per week, with weeks always defined relative to Study Day 1. For example if a patient receives the first dose on a Monday, subsequent doses should be given on Mondays, if possible. If a patient misses an injection, or if dosing on the usual day is not possible, the patient can reschedule the injection provided that 2 doses are administered at least 2 days apart.

Every effort should be made to ensure the previous week's dose is given 7 days prior to a scheduled clinic visit.

Please refer to the Study Drug Manual provided by the Sponsor for more detailed instructions for volanesorsen preparation and administration.

8.2 Other Protocol-Required Drugs

There are no other protocol-required drugs (Section 6.2.5).

8.3 Other Protocol-Required Treatment Procedures

There are no other protocol required treatment procedures for this study.

8.4 Treatment Precautions

There are no specific treatment precautions required for this study.

8.5 Safety Monitoring Rules

Please refer also to the 'Guidance for Investigator' section of the Investigator's Brochure.

For the purposes of safety monitoring baseline is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 (e.g., qualification assessments or assessments from the final visits of ISIS 304801-CS6 and ISIS 304801-CS16 index studies if used for qualification).

In addition to the standard monitoring of clinical safety parameters, the following guidelines are provided for the monitoring of selected parameters chosen based on preclinical and clinical observations.

Confirmation Guidance: At any time during the study (Treatment or Post-Treatment Periods), the initial clinical laboratory results meeting the safety monitoring or stopping criteria presented below **must be confirmed** by performing measurements (ideally in the same laboratory that performed the initial measurement) on new specimens. All new specimen collections should take place as soon as possible (ideally within 3 days of the initial collection). For stopping rules, if the initial laboratory result is observed during the Treatment Period, the results from the retest **must be available** prior to administering the next dose of volanesorsen.

In addition to the safety monitoring parameters listed below, the Sponsor may request confirmation of additional lab values.

Re-dosing Guidance: Patients with initial laboratory test values that reach a stopping rule must not be re-dosed until the re-test results are available. In general, patients who do not meet the stopping rules based upon retest may continue dosing. However, the Investigator and the Sponsor Medical Monitor (or appropriately qualified designee) should confer as to whether additional close monitoring of the patient is appropriate. Reduction in dose or dose frequency may also be initiated as noted in Section 8.7. If any of the stopping criteria described below (refer to Sections 8.6.1 to 8.6.3) are met, the patient will be dose paused or permanently discontinued (as described in the stopping criterion concerned) from further treatment with volanesorsen, and evaluated fully as outlined below and in consultation with the Sponsor Medical Monitor or appropriately qualified designee, and will be followed up in accordance with Section 8.8 of the protocol.

8.5.1 Safety Monitoring for Liver Chemistry Tests

The following rules are adapted from the draft guidance for industry, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," issued by the U.S. Department of Health and Human Services, Food and Drug Administration, July 2009. For a definition of Baseline please refer to guidance in Section 8.5 above.

In the event of an ALT or AST measurement that is > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) at any time during the study (Treatment or Post-Treatment Period), the initial measurement(s) should be confirmed as described above. Additional confirmatory measurements should also be performed if ALT or AST levels increase to 5 x ULN.

Frequency of Repeat Measurements: Patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) should have their liver chemistry tests (ALT, AST, alkaline phosphatase (ALP), international normalized ratio (INR) and total bilirubin) retested at least once-weekly until ALT and AST levels become ≤ 1.2 x ULN or 1.2 x baseline value if the baseline value was > ULN.

Further Investigation into Liver Chemistry Elevations: For patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), the following evaluations should be performed:

1. Obtain a more detailed history of symptoms and prior and concurrent diseases
2. Obtain further history for concomitant drug use (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
3. Obtain a history for exposure to environmental chemical agents and travel
4. Serology for viral hepatitis (HAV IgM, HBsAg, HCV antibody, CMV IgM, and EBV antibody panel)
5. Serology for autoimmune hepatitis (e.g., antinuclear antibody [ANA])

Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic CT or MRI scans, may be performed at the discretion of the Investigator, in consultation with the Sponsor Medical Monitor. Repetition of the above evaluations should be considered if a patient's ALT and/or AST levels reach 5 x ULN.

8.5.2 Safety Monitoring for Platelet Count Results

Actions to be taken in the event of reduced platelet count are shown in Table 2 in Section 8.6.3.

Additional lab tests will be determined by the Sponsor Medical Monitor or designee in consultation with the Investigator.

Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor (See also Stopping Rules Section 8.6.3).

8.5.3 Safety Monitoring for Minor Bleeding Events

Minor bleeding events are those that do not fulfill the criteria for major bleeding or clinically-relevant, non-major bleeding events (which are defined in Section 8.6.3), for example excess bruising, petechiae, gingival bleeding on brushing teeth. If a minor bleeding event occurs, the Investigator must notify the Sponsor Medical Monitor and additional testing of coagulation parameters activated partial thromboplastin time (aPTT), prothrombin time (PT), INR and platelet count should be performed.

8.5.4 Safety Monitoring for Constitutional Symptoms

Patients will be instructed to promptly report any signs of symptoms of fever or constitutional symptoms that may arise during the study and the Investigator should closely evaluate all potential causes, including concomitant illness. Patients that experience persistent constitutional symptoms should be discussed with the Sponsor Medical Monitor or designee to determine whether additional monitoring or laboratory tests are required.

8.5.5 Safety Monitoring for LDL-C Elevations

Beginning at Week 13, laboratory alerts will be in place to notify the Investigator if a patient has a low-density lipoprotein-cholesterol (LDL-C) > 160 mg/dL (> 130 mg/dL for patients with T2DM) on 2 consecutive visits. If this occurs, LDL-C values for this patient will be unblinded for the remainder of the study and the Investigator will be encouraged to initiate/adjust treatment to lower LDL-C according to country-specific guidelines (e.g., initiate statin therapy or increase the statin dose for patients who are already on treatment).

8.5.6 Safety Monitoring for Insulin, Oral Antidiabetic Medication and Glucose

All patients on insulin will monitor their glucose levels with a glucometer as per standard practice guidelines and bring their glucometer or glucometer log printout to every clinic visit. In addition, patients who are not on insulin but use a glucometer should also bring their glucometer and/or glucometer log printout to every clinic visit.

- The Investigator or delegate will review the glucometer reading or printout at every clinic visit to evaluate if fasting pre-breakfast self-monitored plasma glucose values exceed threshold values as per the Safety Monitoring Rules for Hyperglycemia below.

All diabetic patients will note any changes in their insulin dose and /or oral antidiabetic therapy, as well as any hypoglycemic episode they may experience.

- The Investigator or delegate will ask patients at every clinic visit if they made changes in their insulin dose or oral antidiabetic therapy, and if they experienced a hypoglycemic episode.
    - Patients will be instructed on the monitoring and management of hypoglycemic episodes at each visit.
    - Documented symptomatic hypoglycemic episodes should be captured as adverse events in the adverse event CRF. Documented symptomatic hypoglycemia is defined as typical hypoglycemia symptoms accompanied by measured plasma glucose ≤ 70 mg/dL (≤ 3.9 mmol/L).
    - Any changes in insulin dose or oral antidiabetic therapy should be captured into the Concomitant Medication CRF.

8.5.7 Safety Monitoring for Documented Severe Hypoglycemia

A **documented severe hypoglycemic event** is defined as 1 in which the patient requires assistance of another person to obtain treatment for the event and has a plasma glucose level

≤ 70 mg/dL (≤ 3.9 mmol/L). The rescue treatment of hypoglycemia may include IV glucose or buccal or intramuscular glucagon.

The definition of severe symptomatic hypoglycemia includes all episodes in which neurological impairment was severe enough to prevent self-treatment and which were thus thought to place patients at risk for injury to themselves or others. Note that "requires assistance" means that the patient could not help himself or herself. Someone being kind that assists spontaneously the patient when not necessary does not qualify as "requires assistance."

Severe hypoglycemia will be qualified as a SAE only if it fulfills SAE criteria.

If a patient presents with symptoms of hypoglycemia, the Investigator will need to take immediate action to confirm the patient's glucose level and treat the patient accordingly.

The experience of hypoglycemia may vary greatly from patient to patient. However, there are certain classical signs and symptoms, of which patients should be aware as a clue that their blood glucose may be low. Common symptoms include headache, heart pounding, confusion, disorientation, numbness or tingling, pale skin, shakiness or tremulousness, increased appetite, anxiousness or nervousness, lightheadedness or dizziness, sweating, and weakness. Coma could occur if blood sugar correction is not performed.

If patients suspect they might be having a hypoglycemia reaction, they should check their blood glucose using their meters as soon as possible, before treatment if possible, provided they feel it is safe to do so. If there is doubt about safety they should treat the event first, using some sugar, milk, or juice for example, then obtain and record a blood glucose value as soon as possible thereafter. The time and nature of treatment should be noted, and especially if any blood glucose result was before or after treatment. It would be helpful for the patient to note if a contributory factor (e.g., missed or reduced meals, unaccustomed physical activity) occurred earlier in the day of the event.

8.5.8 Safety Monitoring for Hyperglycemia

Upward dose titration and/or addition of any other anti-hyperglycemic agent(s) will not be allowed during the course of the study, unless specific threshold values are met at Week 13 or later and confirmed on subsequent testing (ideally within 1-week of the initial test).

HbA1c is monitored every 3 months throughout the study. In addition, patients on insulin should self-monitor their plasma glucose (SMPG) routinely on a glucometer as per practice guidelines. If a fasting pre-breakfast SMPG value exceeds the specific glycemic limit, the patient should check it again on the following 2 days. If all the fasting pre-breakfast values on 3 consecutive days exceed the specific limit, the patient should contact the Investigator and an unscheduled central laboratory FPG measurement and HbA1c should be performed.

The threshold values are defined as:

- FPG > 270 mg/dL (15.0 mmol/L)
- HbA1c > 9% (for patients with baseline HbA1c < 8% and HbA1c increase of more than 1% from baseline (for patients with baseline HbA1c ≥ 8 and < 9%)

In case of confirmed FPG/HbA1c above the threshold value, the Investigator should ensure that no reasonable explanation exists for insufficient glucose control and in particular that:

- Plasma glucose was actually measured in the fasting condition (i.e., after at least 10 hours fast)
- Absence of intercurrent disease which may jeopardize glycemic control. In case of an emergency (e.g., surgery, infection), the Investigator can take appropriate measures for glycemic control
- Compliance to treatment is appropriate
- Compliance to diet and lifestyle is appropriate

If any of the above can reasonably explain the insufficient glycemic control, the Investigator should consider the following:

- Investigation and treatment of intercurrent disease (to be reported in adverse event (AE)/concomitant medication parts of the e-CRF)
- Stress on the absolute need to be compliant to treatment
- Organize a specific interview with a Registered Dietician or other qualified nutrition professional and stress on the absolute need to be compliant to diet and lifestyle recommendations

A FPG/HbA1c follow-up assessment should be arranged after appropriate action has been taken. If none from the above-mentioned reasons can be found, or if appropriate action fails to decrease FPG/HbA1c under the threshold values, additional medication may be introduced at the Investigator's discretion and according to local guidelines after discussion with the Sponsor Medical Monitor.

8.5.9 Acute Pancreatitis

If a patient has an episode of acute pancreatitis, dosing with Study Drug should be suspended temporarily until the patient is clinically stable. The suitability of the patient for continued dosing and the need for any modification to treatment schedule (refer to Section 8.7) will be determined by the Investigator in consultation with the Study Medical Monitor.

8.6 Stopping Rules

For the purposes of stopping rules baseline is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1.

8.6.1 Stopping Rules for Liver Chemistry Elevations

In the event of laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor,** dosing of a patient with volanesorsen will be stopped permanently; values that are not confirmed due to failure to retest or missing lab values will be presumed confirmed:

1. ALT or AST > 8 x ULN, which is confirmed
2. ALT or AST > 5 x ULN, which is confirmed and persists for ≥ 2 weeks
3. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed **and** total bilirubin > 2 x ULN or INR > 1.5
4. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed, and the new appearance (i.e., onset coincides with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> ULN) felt by the Investigator to be potentially related to hepatic inflammation

8.6.2 Stopping Rules for Renal Function Test Results

In the event of a persistent elevation that is observed over 2 consecutive weeks, for any of the 3 criteria below, dosing of a patient with volanesorsen may be stopped temporarily:

1. Serum creatinine increase that fulfill all of the following criteria: ≥ 0.3 mg/dL (26.5 µmol/L) and ≥ 40% above baseline creatinine values and > ULN
2. Proteinuria, dipstick 2 + (confirmed by dipstick retest and then further confirmed by a quantitative total urine protein measurement of > 1.0 g/24-hour)
3. Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault ≤ 40 mL/min that is confirmed by a 24-hour urine collection

The possible dosing re-initiation or follow-up schedule for any events meeting either of these criteria will be determined by the Investigator **in consultation with** the Sponsor Medical Monitor or designee.

8.6.3 Stopping Rules for Platelet Count Results

Actions to be taken in the event of a low platelet count are summarized in Table 2 below.

In the event of a platelet count less than 75,000/mm^3 that is associated with major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with volanesorsen will be stopped permanently. The follow-up schedule for any events meeting this stopping criterion will be determined by the Investigator in consultation with the Sponsor Medical Monitor.

In the event of any platelet count less than 25,000/mm^3, or a platelet count less than 75,000/mm^3 that occurs while the patient is on dosing at 300 mg every 2 weeks or 150 mg every week then dosing of a patient with volanesorsen will be stopped permanently. Platelet count will be monitored daily until 2 successive values show improvement then monitored every 2-3 days until platelet count is stable.

Administration of steroids is recommended for patients whose platelet count is less than 25,000/mm^3. Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one

0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (**note:** may require continuation with oral steroids after methylprednisolone).

In the event of a platelet count less than 75,000/mm^3, and in the absence of major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with volanesorsen should be suspended temporarily until the platelet count has recovered to> 100,000/mm^3. If dosing is continued it should be at a reduced dose frequency of 300 mg every 2 weeks or a reduced dose of 150 mg per week (refer to Section 8.7). The suitability of the patient for continued dosing will be determined by the Investigator in consultation with the Study Medical Monitor and will be based on factors such as the original rate of decline in the patient's platelet count, whether any bleeding events were experienced by the patient, and the speed of recovery of platelet count upon holding of dosing.

If after the first dosing rechallenge the platelet count again falls below 75,000/mm^3, then dosing of the patient with Study Drug will be stopped permanently.

Following a rechallenge platelet count should be tested every week until count is stable.

Any unreportable platelet count result must be rechecked and determined not to have met a stopping rule before dosing can continue.

If there is no reportable platelet count within 14 days of the last platelet count, the Investigator will contact the patient to hold dosing until a new platelet count is obtained and reviewed.

Definition of Major Bleeding Events (Schulman et al. 2005):

- Fatal bleeding, and/or
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarterial or pericardial, or intramuscular with compartment syndrome, and/or
- Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more within 24 hours, or leading to transfusion of 2 or more units of whole or red cells

Definition of Clinically-Relevant, Non-Major Bleeding Events (Schulman et al. 2005):

1. Multiple-source bleeding
2. Spontaneous hematoma > 25 cm^2
3. Excessive wound hematoma (not injection site related)
4. Macroscopic hematuria (spontaneous or lasting > 24 hours if associated with an intervention)
5. Spontaneous rectal bleeding; epitasis, gingival bleeding, hemoptysis, hematemesis
6. Bleeding after venipuncture for > 5 minutes

Table 2 Actions in Patients with Low Platelet Count

Platelet Count on Rx	Drug Dose	Monitoring
Normal range, > 140K/mm^3	No action	Monitor every 2 weeks
100K-140K/mm^3	No action	Closer observation Monitor every 1-week until stable*
75K-100K/mm^3	Permanently reduce dose frequency to 300 mg every 2 weeks or reduce dose to 150 mg weekly	Closer observation Monitor every 1-week
50K-75K/mm^3	If occurs while on dose of 300 mg every 2 weeks or 150 mg every week then permanently discontinue Study Drug, otherwise dose pause. When platelet count returns to > 100K/mm^3 restart dosing at dose frequency of 300 mg every 2 weeks or 150 mg weekly **only if approved by Sponsor Medical Monitor**	Closer observation Monitor every 2-3 days until 2 successive values show improvement Consider discontinuation of antiplatelet agents/NSAIDS/ anticoagulant medication
25K-50K/mm^3	If occurs while on dose of 300 mg every 2 weeks or 150 mg every week then permanently discontinue Study Drug, otherwise dose pause. When platelet count returns to > 100K/mm^3 restart dosing at dose frequency of 300 mg every 2 weeks or 150 mg weekly **only if approved by Sponsor Medical Monitor**	Closer observation Monitor daily until 2 successive values show improvement then monitor every 2-3 days until platelet count stable Discontinue antiplatelet agents/NSAIDS/anticoagulant medication while platelet count < 50K/mm^3 if possible
< 25K/mm^3	Permanently discontinue Study Drug	Closer observation: Monitor daily until 2 successive values show improvement then monitor every 2-3 days until platelet count stable Steroids recommended** Consider need for hospitalization and referral to hematologist Discontinue antiplatelet agents/NSAIDS/anticoagulant medication while platelet count < 50K/mm^3 if possible

* At least 3 consecutive values measured weekly that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3

** Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (**note**: may require continuation with oral steroids after methyl prednisolone)

8.7 Adjustment of Dose Frequency

Dose adjustments for platelet count reduction must be made in accordance with Section 8.6.3 and Table 2 (above).

Other dose adjustments, including dose interruptions, and/or decreasing the dose or dose frequency will be allowed for safety and tolerability. Any proposed adjustment to treatment

schedule must be discussed with, and approved by, the Study Medical Monitor prior to initiation. Up to 2 adjustments in the treatment schedule may be allowed.

Patients may be dose paused in response to AEs after consultation with Study Medical Monitor.

8.8 Discontinuation of Study Treatment

A patient must permanently discontinue study treatment for any of the following:

- The patient becomes pregnant. Report the pregnancy according to instructions in Section 9.5.4
- The patient withdraws consent
- The patient experiences an AE that necessitates permanent discontinuation of study treatment
- The patient develops laboratory test abnormalities that meet any of the stopping rules listed in Section 8.6

The reason for discontinuation of study treatment must be recorded in the CRF and source documentation.

8.8.1 Follow-up Visits for Early Termination from Treatment Period

Any patient who discontinues early from the Treatment Period should be followed as per the platelet monitoring rules shown in Table 2 in Section 8.6.3 for the first 6 weeks after discontinuing Study Drug. Following this period, if the platelet count is stable (at least 3 consecutive values that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3), the next platelet count should be taken within at least 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug. Patients should also be strongly encouraged to attend applicable landmark visits at Weeks 12, 13, 25, 26, and 50, 52 (calculated based on the time elapsed since Day 1) to collect fasting lipid panels and conduct safety assessments in accordance with the Schedule of Procedures in Appendix A. Any patient who discontinues treatment after Week 44 should also be strongly encouraged to attend a final follow-up visit (Week 65 visit assessments) approximately 13 weeks after their last dose of Study Drug, in addition to the applicable landmark visits.

If the patient declines or is unable to participate in the above, an early termination (ET) visit (Week 52 visit assessments) should be performed at the time of withdrawal, at a minimum, and ideally within 2 weeks from the last dose of Study Drug.

8.8.2 Follow-up Visits for Early Termination from Post-Treatment Follow-up Period

The patient who requests to withdraw from the study during the Post-Treatment Follow-up Period should be encouraged to follow the platelet monitoring rules shown in Table 2 in Section 8.6.3 for the first 6 weeks after discontinuing Study Drug. Following this period, if the platelet count is stable (at least 3 consecutive values that are stable as determined by the Sponsor Medical Monitor and > 100,000/mm^3), the next platelet count should be taken within at least 6 weeks so that patients are monitored for at least 12 weeks after discontinuing Study Drug.

Patients should also be encouraged to undergo a final follow-up visit (Week 65, see Appendix A) prior to leaving the study.

If a patient withdraws due to an AE at any time during the study, the Investigator should arrange for the patient to have appropriate follow-up until the AE has resolved or stabilized.

8.9 Withdrawal of Patients from the Study

Patients must be withdrawn from the study for any of the following:

- Withdrawal of consent
- The patient is unwilling or unable to comply with the protocol

Other reasons for withdrawal of patients from the study might include:

- At the discretion of the Investigator for medical reasons
- At the discretion of the Investigator or Sponsor for noncompliance
- Significant protocol deviation

All efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information, including the reason for withdrawal from study, must be recorded in the CRF.

Any patient who withdraws consent to participate in the study will be removed from further treatment and study observation immediately upon the date of request. These patients should be encouraged to complete the ET study procedures and observations at the time of withdrawal (see Section 8.8 and Appendix A).

For patients withdrawn for reasons other than withdrawal of consent every effort should be made to complete the early termination study procedures and observations at the time of withdrawal (see Section 8.8 and Appendix A).

8.10 Concomitant Therapy and Procedures

The use of concomitant therapies or procedures defined below must be recorded on the patient's CRF. AEs related to administration of these therapies or procedures must also be documented on the appropriate CRF.

8.10.1 Concomitant Therapy

A concomitant therapy is any non-protocol specified drug or substance (including over-the-counter medications, herbal medications and vitamin supplements) administered between signing informed consent and completion of the post-treatment follow-up period. All concomitant medications/treatments and significant non-drug therapies (including supplements and assistive devices) received by a patient, including changes in the patient's current medications, must be recorded in the patient's source documents and CRF. Patients taking over the counter (OTC) omega-3 fatty acids should make every effort to remain on the same brand throughout the study.

Allowed Concomitant Therapy

Any medications deemed necessary by the Investigator are allowed except those listed in the disallowed concomitant therapy.

Disallowed Concomitant Therapy

No lipid lowering therapies (e.g., fibrates, niacin, fish oil or other products containing omega-3 fatty acids [including OTC preparations]), -glucagon-like peptide-1 (GLP-1) agonists, Glybera, or systemic corticosteroids may be started or adjusted after baseline qualification. Doses of existing oral anti-diabetic medication, oral contraceptives, hormone replacement therapy, anticoagulants, or drugs or dietary supplements with potential lipid-altering effects should not be adjusted. Study patients are prohibited from receiving other experimental agents during the study. This includes marketed agents at experimental dosages that are being tested for the treatment of hypertriglyceridemia.

Patients should consult with the Site Investigator or designee prior to initiating any new medication, including non-prescription or herbal compounds or any other non-drug therapy.

8.10.2 Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between signing of informed consent and Week 65 visit.

Disallowed Concomitant Procedure

Plasma apheresis is not allowed during the study.

8.11 Treatment Compliance

Compliance with treatment dosing is to be monitored and recorded by Study Center staff. The Study Center staff is required to document the receipt, dispensing, and return/destruction of volanesorsen. Patients that are self-administering volanesorsen at home must record treatment in a dosing diary that will be reviewed periodically by Study Center staff and the Clinical Monitor.

9. SERIOUS AND NON-SERIOUS ADVERSE EVENT REPORTING

9.1 Sponsor Review of Safety Information

Safety information will be collected, reviewed, and evaluated by the Sponsor in accordance with the Safety Management Plan throughout the conduct of the clinical trial.

9.2 Regulatory Requirements

The Sponsor is responsible for regulatory submissions and reporting to the Investigators of serious adverse events (SAEs) including suspected unexpected serious adverse reactions (SUSARs) per the International Conference on Harmonization (ICH) guidelines E2A and ICH E6. Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines.

Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) will be notified of any SAE according to applicable regulations. The Independent DSMB will be notified of any SAE as specified in the DSMB charter.

In addition to the Investigator's assessment of relatedness, the Sponsor or designee will evaluate the available information and perform an independent assessment of relatedness. While the Sponsor may upgrade an Investigator's decision it is not permissible to downgrade the Investigator's opinion for the purposes of determining whether the SAE meets the definition of a SUSAR.

The following table identifies the SAEs that the Sponsor or designee will not report on an individual basis in an expedited manner because they are anticipated to occur in the study population independent of volanesorsen exposure. The Investigator still has the responsibility to report all SAEs to the Sponsor as described in Sections 9.4.1 to 9.4.3.5.

Table 3 Expected Event for the Protocol Defined Population by Preferred Term and the Expected Incidence

Preferred Term	Expected Incidence in the Protocol Defined Population (Gaudet et al. 2010 and 2013)
Pancreatitis associated events including the PTs of hereditary pancreatitis, pancreatitis, pancreatitis acute, pancreatitis chronic, pancreatitis necrotizing, pancreatitis relapsing	0.2-0.35 events per patient-year

Fatal pancreatitis associated events will be considered as unexpected and are reportable. The Sponsor and DSMB will monitor non-fatal pancreatitis associated SAEs using the incidence rate of the event compared to the rate expected in a non-volanesorsen exposed population. If the aggregate analysis indicates that an event is occurring significantly more frequently or at a greater severity than expected, then the event will be reported.

SAEs not specified in the table will be evaluated on case by case basis to determine whether there is a reasonable possibility that the drug caused the event. If the event is considered by the Sponsor or designee to meet the definition of a SUSAR the event will be reported.

9.3 Definitions

9.3.1 Adverse Event

An adverse event is any unfavorable and unintended sign (including a clinically-significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the study or use of investigational drug product, whether or not the AE is considered related to the investigational drug product.

9.3.2 Adverse Reaction and Suspected Adverse Reaction

An adverse reaction is any adverse event caused by volanesorsen.

A suspected adverse reaction is any adverse event for which there is a reasonable possibility that volanesorsen drug caused the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

9.3.3 Serious Adverse Event (SAE)

A serious adverse event is any adverse event that in the view of either the Investigator or Sponsor, meets any of the following criteria:

- Results in death
- Is life threatening: that is, poses an immediate risk of death at the time of the event

An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Hospitalization is defined as an admission of greater than 24 hours to a medical facility and does not always qualify as an AE
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly or birth defect in the offspring of the patient (whether the patient is male or female)
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

9.4 Monitoring and Recording Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the study (i.e., before informed consent) should be recorded as Medical History and not recorded as AEs unless the pre-existing condition worsened. The Investigator should always group signs and symptoms into a single term that constitutes a **single unifying diagnosis** if possible.

9.4.1 Serious Adverse Events

In the interest of patient safety, and in order to fulfill regulatory requirements**,** all SAEs (regardless of their relationship to volanesorsen) should be reported to the Sponsor or designee within 24 hours of the Study Center's first knowledge of the event. The collection of SAEs will begin after the patient signs the informed consent form and stop at the end of the patient's

follow-up period which is defined as the Week 65 visit. When the Investigator is reporting by telephone, it is important to speak to someone in person versus leaving a message. An Initial Serious Adverse Event Form should be completed and a copy should be faxed to the Sponsor or designee.

Detailed information should be actively sought and included on Follow-Up Serious Adverse Event Forms as soon as additional information becomes available. All SAEs will be followed until resolution. SAEs that remain ongoing past the patient's last protocol-specified follow-up visit will be evaluated by the Investigator and Sponsor. If the Investigator and Sponsor agree the patient's condition is unlikely to resolve, the Investigator and Sponsor will determine the follow-up requirement.

9.4.2 Non-Serious Adverse Events

The recording of non-serious AEs will begin after the patient signs the informed consent form and will stop at the end of the patient's follow-up period, which is defined as the Week 65 visit. The Investigator will monitor each patient closely and record all observed or volunteered AEs on the Adverse Event Case Report Form.

9.4.3 Evaluation of Adverse Events (Serious and Non-Serious)

The Investigator's opinion of the following should be documented on the Adverse Event Case Report Form:

9.4.3.1 Relationship to the Study Drug

The event's relationship to volanesorsen is characterized by 1 of the following:

- **Related:** There is clear evidence that the event is related to the use of volanesorsen, e.g., confirmation by positive rechallenge test
- **Possible:** The event cannot be explained by the patient's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and volanesorsen administration
- **Unlikely/Remote:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to volanesorsen administration and/or exposure suggests that a causal relationship is unlikely (For reporting purposes, Unlikely/Remote will be grouped together with Not Related)
- **Not Related:** The event can be readily explained by the patient's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and volanesorsen

9.4.3.2 Severity

The severity of AEs and SAEs will be graded based on criteria from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010 (refer to Appendix D). Any AE not listed in Appendix D will be graded as follows:

- **Mild:** The event is easily tolerated by the patient and does not affect the patient's usual daily activities
- **Moderate:** The event causes the patient more discomfort and interrupts the patient's usual daily activities
- **Severe:** The event is incapacitating and causes considerable interference with the patient's usual daily activities

If the event is an SAE, then all applicable seriousness criteria must be indicated (criteria listed in Section 9.3.3).

9.4.3.3 Action Taken with Volanesorsen

Action taken with volanesorsen due to the event is characterized by 1 of the following:

- **None:** No changes were made to volanesorsen administration and dose
- **Permanently Discontinued:** Volanesorsen was discontinued and not restarted
- **Temporarily Interrupted, restarted – same dose:** Dosing was temporarily interrupted or delayed due to the AE and restarted at the same dose
- **Reduced schedule:** Dosing frequency was reduced

9.4.3.4 Treatment Given for Adverse Event

Any treatment (e.g., medications or procedures) given for the AE should be recorded on the Adverse Event Case Report Form (treatment should also be recorded on the concomitant treatment or ancillary procedures CRF as appropriate).

9.4.3.5 Outcome of the Adverse Event

If the event is a non-serious AE then the event's outcome is characterized by 1 of the following:

- **AE Persists:** Patient terminates from the trial and the AE continues
- **Recovered:** Patient recovered completely from the AE
- **Became Serious:** The event became serious (the date that the event became serious should be recorded as the Resolution Date of that AE and the Onset Date of the corresponding SAE)
- **Change in Severity** (if applicable): AE severity changed

If the event is a SAE then the event's outcome is characterized by 1 of the following:

- **Ongoing:** SAE continuing
- **Persists (as non-serious AE):** Patient has not fully recovered but the event no longer meets serious criteria and should be captured as an AE on the non-serious AE eCRF (the SAE resolution date should be entered as the date of onset of that AE)
- **Recovered:** Patient recovered completely from the SAE (the date of recovery should be entered as the SAE resolution date)
- **Fatal:** Patient died (the date of death should be entered as the SAE resolution date)

9.4.4 Adjudication Committees

All SAEs that occur during the study that are consistent with a major acute cardiovascular event (MACE) will be adjudicated by a blinded, independent committee as outlined in the MACE Adjudication Charter.

All AEs and SAEs that occur during the study that are consistent with an event of acute pancreatitis will be adjudicated by a blinded, independent committee according to the Atlanta classification of acute pancreatitis (Banks et al. 2013) and as outlined in the Pancreatitis Adjudication Charter. In addition, data for prior episodes of acute pancreatitis or suspected pancreatitis will be collected by review of each patient's medical chart and these events will also be adjudicated.

9.5 Procedures for Handling Special Situations

9.5.1 Abnormalities of Laboratory Tests

Clinically-significant abnormal laboratory test results may, in the opinion of the Investigator, constitute or be associated with an AE. Examples of these include abnormal laboratory results that are associated with symptoms, or require treatment, e.g., bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac arrhythmias due to hyperkalemia. Whenever possible, the underlying diagnosis should be listed in preference to abnormal laboratory values as AEs. Clinically-significant abnormalities will be monitored by the Investigator until the parameter returns to its baseline value or until agreement is reached between the Investigator and Sponsor Medical Monitor. Laboratory abnormalities deemed not clinically-significant (NCS) by the Investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator should not be deemed NCS on the laboratory sheet.

The Investigator is responsible for reviewing and signing all laboratory reports. The signed clinical laboratory reports will serve as source documents and should include the Investigator's assessment of clinical significance of out of range/abnormal laboratory values.

9.5.2 Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the patient is hospitalized; the Study Center must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the patient's consent to participate in the study
- The condition that required the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the patient's consent to participate in the study and the timing of the procedure or treatment
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission

9.5.3 Dosing Errors

Volanesorsen dosing errors should be documented as Protocol Deviations. A brief description should be provided in the deviation, including whether the patient was symptomatic (list symptoms) or asymptomatic, and the event accidental or intentional.

Dosing details should be captured on the Dosing Case Report Form. If the patient takes a dose of volanesorsen that exceeds protocol specifications and the patient is symptomatic, then the symptom(s) should be documented as an AE and be reported per Section 9.4.

Should an overdose occur, the Investigator or designee should refer to the Guidance to Investigator's section of the Investigator's Brochure and contact the Sponsor or designee within 24 hours.

9.5.4 Contraception and Pregnancy

Male patients and female patients of childbearing potential must continue to use appropriate contraception with their partners, or refrain from sexual activity, as described in Section 6.3.1.

If a patient becomes pregnant or a pregnancy is suspected, or if a male patient makes or believes that he has made someone pregnant during the study, then the Study Center staff must be informed immediately. An Initial Pregnancy Form should be submitted to the Sponsor or designee **within 24 hours** of first learning of the occurrence of pregnancy. Follow-up information including delivery or termination is reported on Follow-up Pregnancy Forms and reported within 24 hours.

Payment for all aspects of obstetrical care, child or related care will be the patient's responsibility.

Female patients: If a suspected pregnancy occurs while on the study (including follow-up), a pregnancy test will be performed. The patient with a confirmed pregnancy will be immediately withdrawn from treatment with volanesorsen. However, the patient will be encouraged to complete the post-treatment follow-up portion of the study to the extent that study procedures do not interfere with the pregnancy. Regardless of continued study participation, the study physician will assist the patient in getting obstetrical care and the progress of the pregnancy will be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the Study Center and Sponsor may require access to the mother and infant's medical records for an additional 8 weeks after birth.

Male patients: The progress of the pregnancy in a male patient's partner should be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, **the Study Center and Sponsor may request access to the mother and infant's medical records for an additional 8 weeks after birth**. Follow-up will be performed to the extent permitted by applicable regulations and privacy considerations.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints

For fasting lipid measurements, the values at Month 3 analysis time point are defined as the average of Week 12 (Day 78) and Week 13 (Day 85) fasting assessments, the values of Month 6 analysis time point is at the end of Month 6 are defined as the average of Week 25 (Day 169) and Week 26 (Day 176) fasting assessments, and the values at the Month 12 analysis time point are defined as the average of Week 50 (Day 344) and Week 52 (Day 358) fasting assessments.

10.1.1 Efficacy Endpoints

- Percent change and absolute change from baseline in fasting TG
- Frequency and severity of patient reported abdominal pain during the treatment period
- Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-HDL-C, apoB, HDL-C, apolipoprotein A-1 (apoA-1), VLDL-C, and LDL-C
- Percent change from baseline in fasting total apolipoprotein C-III
- Quality of Life questionnaires (EQ-5D, SF-36)
- Adjudicated acute pancreatitis event rate
- Other symptoms: eruptive xanthoma, lipemia retinalis

10.1.2 Safety Endpoints

- Adverse events including adjudicated events of pancreatitis and MACE
- Vital signs and weight
- Physical examinations
- Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis)
- Echocardiography
- Electrocardiograms (ECGs)
- Use of concomitant medications
- MRIs

10.2 Sample Size

No sample size calculations were performed as this is an open-label study.

10.3 Populations

Full Analysis Set (FAS): All patients who are enrolled and have a baseline TG assessment. The FAS represents the practically-feasible intent-to-treat (ITT) population as delineated in ICH Guideline E9.

Per Protocol Set (PPS): Subset of the FAS who received 9 of first 13 scheduled doses of volanesorsen and with no significant protocol deviations that would be expected to affect efficacy and PD assessments. The detailed criteria will be specified and finalized prior to the final database lock.

Safety Set: All patients who are enrolled and receive at least 1 dose of volanesorsen.

PK Population: All patients who are enrolled, receive at least 1 dose of volanesorsen, and have at least 1 evaluable PK sample collected, analyzed, and reported.

10.4 Definition of Baseline

Definitions of baseline are given below for the purposes of the final analysis.

For fasting lipid measurements, 2 baselines are defined for each patient in Groups 1 and 2: Group 1 (ISIS 304801-CS6) or Group 2 (ISIS 304801-CS16) index study baseline and the baseline in this open-label study, which is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 (e.g., qualification assessments or assessments from final visit of the ISIS 304801-CS6 or ISIS 304801-CS16 index studies if used for qualification).

For other measurements, baseline for patients on active treatment in the ISIS 304801-CS6 or ISIS 304801-CS16 index study will be the ISIS 304801-CS6 or ISIS 304801-CS16 index study baseline. For patients on placebo in the ISIS 304801-CS6 or ISIS 304801-CS16 index study, baseline for safety will be the last non-missing assessment prior to the first dose of Study Drug.

10.5 Interim Analysis

An interim analysis may be conducted after the last patient's Week 13 visit of the open-label study or after the database of the ISIS 304801-CS6 and ISIS 304801-CS16 index studies are locked and unblinded. Both safety and efficacy information from this open-label study may be summarized during this interim analysis. Efficacy analyses will be detailed in the SAP.

10.6 Planned Methods of Analysis

All eCRF data, lab data transfers, as well as any outcomes derived from the data, will be provided in the patient data listings. Patient data listings will be presented for all patients enrolled into the study. Descriptive summary statistics including n, mean, median, standard deviation, standard error, interquartile range (25th percentile, 75th percentile), and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data by treatment group. Where appropriate, p-values will be reported. All statistical tests will be conducted using 2-sided tests with 5% Type I error rates unless otherwise stated.

All efficacy endpoints will be assessed in the FAS and PPS. All safety assessments will be performed on the Safety Set. PK endpoints will be assessed in the PK Set as applicable.

10.6.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics by treatment group. The patient disposition will be summarized by treatment group of the index studies. All patients enrolled will be included in a summary of patient disposition.

10.6.2 Safety Analysis

Treatment duration and amount of Study Drug received will be summarized by treatment group of the index studies.

Patient incidence rates of AEs will be tabulated by MedDRA system organ class, MedDRA preferred term, and treatment group of the index studies. Narratives of treatment-emergent deaths, serious and significant AEs, including early withdrawals due to AEs, will also be provided.

All treatment-emergent AEs, all treatment-emergent AEs potentially related to Study Drug, all treatment-emergent serious AEs, and all treatment-emergent serious AEs potentially related to Study Drug will be summarized.

Injection Site Reactions (ISRs) will be summarized by treatment group of the index studies, MedDRA preferred term and severity.

Independently adjudicated events of MACE and pancreatitis will be summarized by treatment group of the index studies.

Laboratory tests to ensure patient safety including chemistry panel, complete blood count (CBC) with differential, coagulation panel, IM, complement etc., will be summarized by study visits by treatment group of the index studies.

These safety variables will also be presented as change and percent change from baseline over time after Study Drug administration, as appropriate.

Vital signs, weight, ECG measures, echocardiography assessments, and MRI assessments will be tabulated by treatment group of the index studies.

10.6.3 Efficacy Analysis

Percent change and change from baseline to Month 3, Month 6, and Month 12 in fasting TG will be summarized by treatment group of the index studies. Response rate of patients with fasting plasma TG < 750 mg/dL or achieving fasting TG $\geq 40\%$ reduction from baseline at Month 3, Month 6, and Month 12 will be summarized. Response analysis will also be conducted using a range of fasting plasma TG thresholds for determination of responder status.

Percent change and change from baseline to Month 3, Month 6, and Month 12 will also be summarized by treatment group of the index studies for other fasting lipid measures including non-HDL-C, apoB, HDL-C, apoA-1, VLDL-C, and LDL-C, total cholesterol, and fasting total apoC-III.

The incremental effects of volanesorsen on lipid measures will be explored and the association between changes in lipid parameters and total amount of drug received will be examined, as appropriate.

Frequency and severity of patient reported abdominal pain, adjudicated acute pancreatitis event rate, quality of life assessments, and comparison of other symptoms including eruptive xanthomas and lipemia retinalis will be summarized by treatment group of the index studies.

Additional details of the analyses to be conducted will be provided in the SAP.

10.6.4 Pharmacokinetic and Immunogenicity Analysis

10.6.4.1 Pharmacokinetic Analysis

For all patients, pre-dose and post-treatment volanesorsen plasma concentrations will be summarized using descriptive statistics, with stratification for Group 1 and 2 patients by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16 and IM status.

For patients in the PK subgroup only, non-compartmental PK analysis of volanesorsen will be carried out on each individual patient data set using data collected in the open-label study from the intensive PK subgroup, following a single-dose (i.e., single-dose PK) or multiple doses (i.e., steady-state PK), depending on their earlier treatment in the index studies (Group 1 and 2 patients). On Week 1 Day 1 of the open-label study, patients who received placebo in the index study (and all patients in Group 3) will receive the first treatment of volanesorsen (single-dose PK), while patients who received volanesorsen in the index studies had been on volanesorsen treatment for 12 months (ISIS 304801-CS6) or 6 months (ISIS 304801-CS16), thus the PK data collected from these patients reflect steady-state PK. The maximum observed drug concentration (C_{max}) and the time taken to reach C_{max} (T_{max}) will be obtained directly from the concentration-time data. Area under the plasma concentration-time curve from time zero to 24 hours ($AUC_{0\text{-}24hr}$) will be calculated using the linear trapezoidal rule. Apparent systemic (plasma) clearance after SC administration ($CL_{0\text{-}24hr}/F_{0\text{-}24hr}$) will be calculated from $CL_{0\text{-}24hr}/F_{0\text{-}24hr}$ = Actual Dose/$AUC_{0\text{-}24hr}$. Mean residence time (MRT) from time zero to 24 hours after the SC administration will be calculated from the equation, $MRT_{0\text{-}24hr} = AUMC_{0\text{-}24hr}/AUC_{0\text{-}24hr}$, where $AUMC_{0\text{-}24hr}$ is the area under the moment plasma concentration-time curve from time zero to 24 hours after the SC administration. Other PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist.

Plasma PK parameters will be summarized using descriptive statistics, with and without stratification by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16 and IM status. Additional details regarding the PK analysis will be described in the SAP.

Population PK, PK/PD, and covariate analysis may be performed if deemed appropriate, and results will be reported separately.

10.6.4.2 Immunogenicity Analysis

Immunogenicity (IM) results (screen positive/negative, confirmed positive/negative or not evaluable, and when applicable, titer of anti-volanesorsen antibodies) before, during, and after treatment with Study Drug (volanesorsen) (i.e., sample [anti-drug antibody] ADA status) will be

listed by their prior treatment in study ISIS 304801-CS6 or ISIS 304801-CS16 (Groups 1 and 2) and study day. Subject ADA status (positive/negative or not evaluable) for all evaluable patients, along with the study day associated with the first positive IM status emerged (T_{first}, i.e., onset of ADA development), the last positive IM status observed (T_{last}), the duration of ADA response (number of days between T_{first} and T_{last}) if appropriate, the last ADA sample collection day, and subject - peak titer if applicable, will be listed by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16 (Groups 1 and 2) and study day. Subjects with positive anti-volanesorsen antibody status may be further classified (when applicable) as being either 'persistent', 'transient', or 'not determinable', if deemed appropriate.

Additionally, the sample and subject IM incidence (number) and incidence rate (percent) will be summarized as the total number and percent of evaluated subjects with antibody negative, positive, and unknown status by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16. Furthermore, onset, duration, and titer of the ADA response, if applicable, will be summarized as median, quartiles (25% and 75%), and range.

Additional details regarding the IM data analysis will be described in the SAP.

Potential relationships between immunogenicity results (e.g., IM status) and selected efficacy (e.g., % change in fasting TG from baseline at 3-, 6-, and 12-month endpoints), safety, and PK (e.g., C_{trough}) measures will be evaluated using graphical analysis and statistical analysis. These analyses will be either conducted and included in the study report, or data pooled and analyzed from all available Phase 2 and 3 studies and reported separately.

11. INVESTIGATOR'S REGULATORY OBLIGATIONS

11.1 Informed Consent

The written informed consent document should be prepared in the language(s) of the potential patient population, based on an English version provided by the Sponsor.

Before a patient's participation in the trial, the Investigator is responsible for obtaining written informed consent from the patient after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific qualification procedures or any Study Drug are administered. The patient must be given sufficient time to consider whether to participate in the study.

The acquisition of informed consent and the patient's agreement or refusal to notify his/her primary care physician should be documented in the patient's medical records and the informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion (not necessarily an Investigator). The original signed informed consent form should be retained in the Study Master File and in any other locations required by institutional policy, and a copy of the signed consent form should be provided to the patient.

11.2 Ethical Conduct of the Study

The Guidelines of the World Medical Association (WMA) Declaration of Helsinki dated October 2002 the applicable regulations and guidelines of current Good Clinical Practice (GCP) as well as the demands of national drug and data protection laws and other applicable regulatory requirements will be strictly followed.

11.3 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent form, other written patient information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by the Sponsor before recruitment of patients into the study and shipment of volanesorsen. A copy of the written approval of any other items/materials that must be approved by the Study Center or IEC/IRB must also be received by the Sponsor before recruitment of patients into the study and shipment of Study Drug. The Investigator's Brochure must be submitted to the IEC/IRB for acknowledgement.

The Investigator must submit to and, where necessary, obtain approval from the IEC/IRB, for all subsequent protocol amendments and changes to the informed consent document. The Investigator should notify the IEC/IRB of deviations from the protocol in accordance with ICH GCP Section 4.5.2. The Investigator should also notify the IEC/IRB of serious adverse events occurring at the Study Center and other adverse event reports received from the Sponsor, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study. Copies of the Investigator's reports, all IEC/IRB submissions and the IEC/IRB continuance of approval must be sent to the Sponsor.

11.4 Patient Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained. On the case report forms (CRF) or other documents submitted to the Sponsor, patients should be identified by unique initials and a patient study number only. Documents that are not for submission to the Sponsor (e.g., signed informed consent forms) should be kept in strict confidence by the Investigator.

In compliance with Federal and local regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the patient to permit named representatives to have access to his/her study-related records without violating the confidentiality of the patient.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments

Protocol amendments must be made only with the prior approval of the Sponsor. Agreement from the Investigator must be obtained for all protocol amendments and amendments to the informed consent document. The regulatory authority and IEC/IRB must be informed of all amendments and give approval for any amendments likely to affect the safety of the patients or the conduct of the trial. The Investigator **must** send a copy of the approval letter from the IEC/IRB to the Sponsor.

12.2 Study Termination

The Sponsor reserves the right to terminate the study according to the terms of the site contract. The Investigator reserves the right to terminate their participation in the study, according to the terms of the site contract. The Investigator/Sponsor should notify the IEC/IRB in writing of the trial's completion or early termination and send a copy of the notification to the Sponsor.

12.3 Study Documentation and Storage

An electronic case report form (eCRF) utilizing an Electronic Data Capture (EDC) application will be used for this study.

The Investigator should ensure that all appropriately qualified persons to whom he/she has delegated trial duties are recorded on a Sponsor-approved Delegation of Site Responsibilities Form.

Source documents are original documents, data, and records from which the patient's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, imaging, and correspondence. In this study, CRFs may not be used as source documents.

The Investigator and Study Center staffs are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation in accordance with Section 8 of the ICH Guidelines (E6), suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Elements should include:

- Patient files containing completed CRFs, informed consents, and supporting copies of source documentation
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation and all correspondence to and from the IEC/IRB and the Sponsor
- If volanesorsen supplies are maintained at the Study Center, proof of receipt, volanesorsen Accountability Record, Return of volanesorsen for Destruction, final study volanesorsen reconciliation, and all volanesorsen-related correspondence

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

No study document should be destroyed without prior written agreement between the Sponsor or and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor.

12.4 Study Monitoring

The Sponsor representative and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the trial (e.g., CRFs and other pertinent data) provided that patient confidentiality is respected.

The Sponsor monitor is responsible for inspecting the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to patient medical records and other study-related records needed to verify the entries on the CRFs.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's Clinical Quality Assurance Department. Inspection of Study Center facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the trial conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

To ensure the quality of clinical data a clinical data management review will be performed on patient data received by the Sponsor. During this review, patient data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or Study Center notifications will be sent to the Study Center for completion and return to Sponsor.

The Principal Investigator will sign and date the indicated places on the CRF. These signatures will indicate that the principal Investigator inspected or reviewed the data on the CRF, the data queries, and the Study Center notifications, and agrees with the content.

12.5 Language

Case report forms must be completed in English. Generic names for concomitant medications should be recorded in English if possible, unless it is a combination drug, then record the trade name in English.

All written information and other material to be used by patients and investigative staff must use vocabulary and language that are clearly understood.

12.6 Compensation for Injury

The Sponsor maintains appropriate insurance coverage for clinical trials and will follow applicable local compensation laws. Patients will be treated and/or compensated for any study-related illness/injury in accordance with the information provided in the Compensation for Injury section of the Informed Consent document.

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14. APPENDICES

Appendix A Schedule of Procedures

Appendix A Schedule of Procedures

Study Period		Screen/ Run In[a]	Qual[a]	Treatment Period																							Post Treatment Follow-up		
Study Week		-8 to -2	-2 to -1	Wk 1		Wk 2.5	Wk 4	Wk 6	Wk 8	Wk 10	Month 3		Wk 15 & 17	Wk 19	Wk 21 & 23	Month 6		Wk 28 & 30	Wk 32	Wk 34 & 36	Wk 38	Wk 40 & 42	Wk 44	Wk 46 & 48	Month 12		Wk 54 & 56	Wk 58	Wk 65
											Wk 12	Wk 13				Wk 25	Wk 26								Wk 50	Wk 52 or ET			
Study Day		-56 to -15	-14 to -7	1	2	11	22	36	50	64	78	85	99 & 113	127	141 & 155	169	176	190 & 204	218	232 & 246	260	274 & 288	302	316 & 330	344	358	372 & 386	400	449
Visit Window+/- Days		0	0	0	0	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	7	7
Informed Consent		X	X																										
Outpatient Visit		X	X	X	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X	X[j]	X[j]	X[j]	X[j]	X	X[j]	X[j]	X[j]	X	X[j]	X[j]	X[j]	X[j]	X	X[j]	X[j]	X
Inclusion/Exclusion Criteria		X	X																										
Vital Signs + body weight (+ height on Day 1 only)		X	X	X			X		X			X					X				X					X			X
Physical Examination		X		X								X					X				X					X			X
12- lead ECG (triplicate)		X										X					X				X					X			X
MRI (liver/spleen)		X																								X[k]			
Echocardiography		X															X[k]									X[k]			
Blood Draw (Fasting)[c]	Chemistry Panel	X	X	X			X		X			X		X			X		X		X		X			X		X	X
	CBC with Differential[b]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Serum Lipid Panel	X	X	X			X		X		X	X				X	X				X				X	X			X
	Coagulation (aPTT, PT, INR)	X	PG						X			X					X				X					X			
	hsCRP, HbA1c, FPG, and de-lipidated free glycerol			X								X					X									X			X
	Sedimentation Rate			X								X					X									X			X
	Complement (C5a, Bb)			X								X					X									X			X
	Plasma PK - Volanesorsen			X[l]	X		X		X			X					X				X					X			X
	Anti-Volanesorsen Antibodies			X			X		X			X					X				X					X			X
	FSH (women only, if applicable)	X																											
	Serum Pregnancy Test[d]	X	X				X		X			X		X			X		X		X		X			X		X	X
	Archived Serum & Plasma Samples[e]			X					X			X					X									X			X

Appendix A Schedule of Procedures *Continued*

Study Period	Screen/ Run In[a]	Qual[a]	Treatment Period																								Post Treatment Follow-up		
Study Week	-8 to -2	-2 to -1	Wk 1		Wk 2.5	Wk 4	Wk 6	Wk 8	Wk 10	Month 3		Wk 15 & 17	Wk 19	Wk 21 & 23	Month 6		Wk 28 & 30	Wk 32	Wk 34 & 36	Wk 38	Wk 40 & 42	Wk 44	Wk 46 & 48	Month 12		Wk 54 & 56	Wk 58	Wk 65
										Wk 12	Wk 13				Wk 25	Wk 26								Wk 50	Wk 52 or ET			
Study Day	-56 to -15	-14 to -7	1	2	11	22	36	50	64	78	85	99 & 113	127	141 & 155	169	176	190 & 204	218	232 & 246	260	274 & 288	302	316 & 330	344	358	372 & 386	400	449
Visit Window+/- Days	0	0	0	0	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	7	7
Urinalysis[c]	X	X	X[m]			X		X			X[m]		X[m]			X[m]		X[m]		X[m]		X[m]			X[m]		X[m]	X[m]
Fundus Photography[f]	X																								X[k]			
Genetic testing for FCS diagnosis (if not available in medical history)[g]	X																											
Weekly Study Drug: SC Injection			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Symptom Diary (weekly)	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Assessment(s)			X								X					X									X			X
Food/Drink Diary (quarterly)[h]			X								X					X									X			X
Diet/Alcohol Counseling[i]	X	X	X			X		X			X					X				X					X		X	X
Adverse Events	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a Screening and Qualification (Group 3) procedures performed (Please refer to Sections 3.4, 4.1, and 6.1.2)

b Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1-week and determined not to have met a stopping rule before dosing can continue. If there is no reportable platelet count within 14 days of the last platelet count, the Investigator will contact the patient to hold dosing until a new platelet count is obtained and reviewed. All platelet count results will be promptly reviewed by the Investigator to ensure that the count has not met the stopping rule and to determine whether the rate of decline is suggestive that the patient could be approaching the dose pause rule of 75,000/mm^3. Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor

Appendix A Schedule of Procedures Continued

Legend Text *Continued*

c Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours. During treatment period urine and blood samples will be collected prior to Study Drug administration. Does not apply to 24-hour PK blood draw

d Females of childbearing potential only

e Serum and plasma samples will be collected and stored for follow-up exploration of laboratory findings and/or adverse events (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.) in this or subsequent clinical studies of volanesorsen

f If possible, fundus photography should be completed prior to administration of the first dose of Study Drug (Group 2 [ISIS 304801-CS16 rollover patients] and Group 3) and repeated at Week 52 (Please refer to Section 6.2.2.2)

g Genetic testing can be conducted for study qualification (Group 2 [ISIS 304801-CS16 rollover patients] and Group 3); genetic testing will only be conducted if allowed in the geographic region and only after the patient has given specific written informed consent for genetic testing

h In addition to diary, patients will be contacted at random times during the study to review their current eating and drinking habits

i To reinforce compliance to the diet and alcohol restrictions. Random diet/alcohol assessments (phone visits) will also be performed by dietician or study personnel

j Assessments and procedures to be conducted by either a home healthcare nurse, or the Study Center as arranged by the Study Center personnel

k A ± 7-day window is allowed for MRI, echocardiography procedures and fundus photography

l Full or abbreviated PK profile (see Appendix C)

m Expanded urinalysis (see Appendix B)

Appendix B List of Laboratory Analytes

Appendix B List of Laboratory Analytes

Based on emerging data from this or future studies, additional tests not listed below may be performed on stored samples to better characterize the profile of volanesorsen or other similar oligonucleotides.

Clinical Chemistry Panel

- Sodium
- Potassium
- Chloride
- Bicarbonate
- Total protein
- Albumin
- Calcium
- Magnesium
- Phosphorus
- Glucose
- BUN
- Creatinine
- Uric Acid
- Total bilirubin
- Direct (conjugated) bilirubin
- Indirect (unconjugated) bilirubin
- ALT
- AST
- Alkaline phosphatase

Coagulation

- aPTT (sec)
- PT (sec)
- INR

Lipid Panel

- Total Cholesterol
- LDL-C
- HDL-C
- Triglycerides
- Non-HDL-C
- VLDL-C
- apoA-1
- apoB
- apoC-III

Hematology

- Red blood cells
- Hemoglobin
- Hematocrit
- MCV, MCH, MCHC
- Platelets
- White blood cells
- WBC Differential (% and absolute)
  - Neutrophils
  - Eosinophils
  - Basophils
  - Lymphocytes
  - Monocytes

Pharmacokinetics[1] & Immunogenicity

- Volanesorsen levels in plasma
- Anti-volanesorsen antibodies in plasma

Other Assessments

- hsCRP
- Sedimentation Rate
- C5a, Bb
- De-lipidated free glycerol
- HbA1c, FPG

Urinalysis

- Color
- Appearance
- Specific gravity
- pH
- Protein
- Blood
- Ketones
- Urobilinogen
- Glucose
- Bilirubin
- Leukocyte esterase
- Nitrate
- Microscopic examination[2]

Additional Measures for Expanded Urinalysis

- Total protein (quantitative)
- Microalbumin
- β2-microglobulin

1 Plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, IM testing (or possibly for purposes of IM assay development and/or validation), or to assess other actions of volanesorsen with plasma constituents

2 Will be performed on abnormal findings unless otherwise specified

Appendix C Pharmacokinetic Sampling Schedule

Appendix C Pharmacokinetic Sampling Schedule

Blood samples for the determination of plasma volanesorsen concentrations will be collected prior to dosing, and at various times throughout the dosing and post-treatment follow-up period as noted in the tables below.

PK Sampling Schedule (All Patients except PK Subgroup)

Week	**Wk 1**	**Wk 4**	**Wk 8**	**Wk 13**	**Wk 26**	**Wk 38**	**Wk 52**	**Wk 65**
Study Day	**D1**	**D22**	**D50**	**D85**	**D176**	**D260**	**D358**	**D449**
Visit Window +/- Days	0	2	2	2	2	3	2	7
Time Point	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime

PK Sampling Schedule (PK Subgroup only*)

Week	**Wk 1**	**Wk 1**	**Wk 4**	**Wk 8**	**Wk 13**	**Wk 26**	**Wk 38**	**Wk 52**	**Wk 65**
Study Day	**D1**	**D2**	**D22**	**D50**	**D85**	**D176**	**D260**	**D358**	**D449**
Visit Window +/- Days	0	0	2	2	2	2	3	2	7
Time Point	Pre-dose, 1, 2, 3, 4, 6, 8, and 12 hrs post-dose	24 hrs post-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime

* Patients at selected sites will be asked to participate in the extended 24-hour PK profile beginning on Study Day 1. Participation is optional

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

The following grading recommendations for adverse events relating to lab test abnormalities are based upon the **Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010**

Adverse Event	Mild	Moderate	Severe
Hematology			
aPTT prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage
Eosinophils increased†	650 – 1,500 cell/mm^3	1,501 - 5,000 cell/mm^3	>5,000 cell/mm^3
Fibrinogen decreased	<1.0 - 0.75 x LLN or <25% decrease from baseline	<0.75 - 0.5 x LLN or 25 - <50% decrease from baseline	<0.5 x LLN or ≥50% decrease from baseline
Hemoglobin decreased (Anemia)	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated
Hemoglobin increased	Increase in >0 - 2 g/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 g/dL above ULN or above baseline if baseline is above ULN	Increase in >4 g/dL above ULN or above baseline if baseline is above ULN
INR increased	>1 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation
Lymphocyte count decreased	<LLN - 800/mm^3; <LLN - 0.8 x 10^9/L	<800 - 500/mm^3; <0.8 - 0.5 x 10^9 /L	<500 /mm^3; <0.5 x 10^9 /L
Lymphocyte count increased	-	>4000/mm^3 - 20,000/mm^3	>20,000/mm^3
Neutrophil count decreased	<LLN - 1500/mm^3; <LLN - 1.5 x 10^9 /L	<1500 - 1000/mm^3; <1.5 - 1.0 x 10^9 /L	<1000/mm^3; <1.0 x 10^9 /L
Platelet count decreased	<LLN - 75,000/mm^3; <LLN - 75.0 x 10^9 /L	<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9 /L	<50,000/mm^3; <50.0 x 10^9 /L
White blood cell decreased	<LLN - 3000/mm^3; <LLN - 3.0 x 10^9 /L	<3000 - 2000/mm^3; <3.0 - 2.0 x 10^9 /L	<2000/mm^3; <2.0 x 10^9 /L
Chemistry			
Acidosis	pH <normal, but >=7.3	-	pH <7.3
Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Alkalosis	pH >normal, but ≤7.5	-	pH >7.5
Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 x ULN
Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

Adverse Event	Mild	Moderate	Severe
Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer
CD4 lymphocytes decreased	<LLN - 500/mm^3; <LLN - 0.5 x 10^9 /L	<500 - 200/mm^3; <0.5 - 0.2 x 10^9 /L	<200/mm^3; <0.2 x 10^9 /L
CPK increased*	>ULN - <6 ULN	6 - 10 x ULN	>10 x ULN
Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 x ULN
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 mg/dL; >3.1 mmol/L; Ionized calcium >1.6 mmol/L; hospitalization indicated
Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 mg/dL; >13.9 mmol/L; hospitalization indicated
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0; hospitalization indicated
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 mg/dL; >1.23 mmol/L
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 mmol/L; hospitalization indicated
Hyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 mg/dL; <1.75 mmol/L; Ionized calcium <0.9 mmol/L; hospitalization indicated
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 mg/dL; <3.0 mmol/L	<40 mg/dL (<2.2 mmol/L) AND requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions‡
Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 mmol/L; hospitalization indicated
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 mg/dL; <0.4 mmol/L
Hyponatremia	<LLN - 130 mmol/L	-	<130 mmol/L
Hypophosphatemia	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 mg/dL; <0.6 mmol/L
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

Adverse Event	Mild	Moderate	Severe
Urine			
Proteinuria Adults Children	1+ proteinuria; urinary protein <1.0 g/24 hrs -	2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs; Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Urinary protein ≥3.5 g/24 hrs; Urine P/C >1.9
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated

†Grading for this parameter is derived from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007

*Grading for this parameter is derived from the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0, Nov 2014

‡Modified for consistency with the ADA and Endocrine Society Guidelines (Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. Diabetes Care 2013;36:1384-95)

Sponsor:
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Collaborator:
Akcea Therapeutics
55 Cambridge Parkway, Suite 100
Cambridge, MA 02142

ISIS 304801-CS7

The APPROACH Open Label Extension Study

Volanesorsen (ISIS 304801)

An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol Amendment 4 –6 June 2016

EudraCT No: 2015-003755-21

ISIS 304801-CS7

The APPROACH Open Label Extension Study

Volanesorsen (ISIS 304801)

An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol Amendment 4 – 6 June 2016

Protocol History:

Original Protocol:	28 August 2015
Protocol Amendment 1:	2 February 2016
Protocol Amendment 2:	22 April 2016
Protocol Amendment 3:	9 May 2016

Sponsor:

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[redacted] M.D., M.B.A.

[redacted]

Ionis Protocol Number: ISIS 304801-CS7

Protocol Amendment 4

EudraCT No: 2015-003755-21

Clinical Phase: 3

The APPROACH Open Label Extension Study

Volanesorsen (ISIS 304801)

An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

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Cambridge, MA 02142

Date: 6 June 2016

Confidentiality Statement

This document contains confidential information of Ionis Pharmaceuticals, Inc., that must not be disclosed to anyone other than the recipient study staff and members of the independent ethics committee, institutional review board, or authorized regulatory agencies. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc.

Protocol Signature Page

Protocol Number: ISIS 304801-CS7

Protocol Title: An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Amendment: Amendment 4

Date: 6 June 2016

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)", dated 6 June 2016, and agree to conduct the study as described herein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice (E6).

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc.

Investigator's Signature

Investigator's Name *(please print)*

Date (DD Month YYYY)

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PROTOCOL AMENDMENT

Protocol Number:	ISIS 304801-CS7
Protocol Title:	An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Amendment Number:	4
Amendment Date:	6 June 2016

The purpose of this protocol amendment is to implement the following modifications to Protocol ISIS 304801-CS7 Amendment 3 dated 9 May 2016:

1. To add hematology blood draws so that platelet counts are measured every 2 weeks during the treatment period and every 2 weeks for the first 6 weeks after the last dose of Study Drug.
2. To update the platelet safety monitoring rules (shown in Table 2).
3. To add language to indicate that if there is no reportable platelet count within 14 days of the last platelet count, the Investigator will contact the patient to hold dosing until a new platelet count is obtained and reviewed.
4. To add language to indicate that all platelet count results will be promptly reviewed by the Investigator to ensure that the count has not met the stopping rule and to determine whether the rate of decline is suggestive that the patient could be approaching the dose pause rule of 75,000/mm^3.
5. To change the platelet dose pause/stopping rule from 50,000/mm^3 to 75,000/mm^3 and to add that when platelet count returns to ≥ 100,000/mm^3 dosing may be continued but at a reduced dose frequency of 300 mg every 2 weeks or a reduced dose of 150 mg per week and only if approved by the Sponsor Medical Monitor.
6. To add language to indicate that in the event of any platelet count less than 25,000/mm^3, or a platelet count less than 50,000/mm^3 that occurs while the patient is on dosing at 300 mg every 2 weeks or 150 mg per week, then dosing of a patient with volanesorsen will be stopped permanently. Platelet count will be monitored daily until 2 successive values show improvement then monitored every 2-3 days until platelet count is stable.
7. To add language to indicate that administration of steroids is recommended for patients whose platelet count is less than 25,000/mm^3 and to provide treatment guidelines for the administration of steroids.
8. To add a Table summarizing actions to be taken in the event of a low platelet count.

9. To add language to indicate that patients will receive a suitable dose or dose frequency of volanesorsen, when they enter this CS7 study, based on safety/tolerability or non-safety/tolerability dosing rules.

Minor administrative changes or corrections (not included in the list of changes) have been made throughout the protocol in order to improve the overall clarity of the protocol but these changes do not impact the study design.

The following table provides a summary list of changes to the protocol:

Protocol Section	Description of Change	Rationale
Section 6.1.2 Treatment Period Section 6.1.4 Post-Treatment Period Appendix A Schedule of Procedures	Hematology blood draws added to Weeks 2.5, 6, 10, 15, 17, 21, 23, 28, 30, 34, 36, 40, 42, 46, 48, 50, 54, 56 and removed from Weeks 16, 22, 29, 35, 41, 47 and 51.	To implement more frequent evaluation of platelet counts to assess platelet fluctuations during the course of the study and to increase platelet count monitoring for safety purposes
Section 8.5.2 Safety Monitoring for Platelet Count Results	Actions to be taken in the event of reduced platelet count are shown in Table 2 in Section 8.6.3.	To increase platelet count monitoring for safety purposes
Section 6.2.1 Laboratory Assessments Section 8.6.3 Stopping Rules for Platelet Count Results Appendix A Schedule of Procedures	If there is no reportable platelet count within 14 days of the last platelet count, the Investigator will contact the patient to hold dosing until a new platelet count is obtained and reviewed.	To increase platelet count monitoring and provide added patient safety regarding ISIS 304801 dose exposure
Section 6.2.1 Laboratory Assessments Appendix A Schedule of Procedures	All platelet count results will be promptly reviewed by the Investigator to ensure that the count has not met the stopping rule and to determine whether the rate of decline is suggestive that the patient could be approaching the dose pause rule of 75,000/mm^3.	To increase platelet count monitoring for safety purposes
Section 8.6.3 Stopping Rules for Platelet Count Results	Dose pause/ stopping rule changed from 50,000/mm^3 to 75,000/mm^3 and when platelet count returns to ≥ 100,000/mm^3 dosing may be continued but at a reduced dose frequency of 300 mg every 2 weeks or a reduced dose of 150 mg per week and only if approved by the Sponsor Medical Monitor.	To increase platelet count monitoring and provide added patient safety regarding ISIS 304801 dose exposure

<table>
<tr><th>Protocol Section</th><th>Description of Change</th><th>Rationale</th></tr>
<tr><td>Section 8.6.3 Stopping Rules for Platelet Count Results</td><td>In the event of any platelet count less than 25,000/mm^3, or a platelet count less than 50,000/mm^3 that occurs while the patient is on dosing at 300 mg every 2 weeks or 150 mg per week, then dosing of a patient with volanesorsen will be stopped permanently. Platelet count will be monitored daily until 2 successive values show improvement then monitored every 2-3 days until platelet count is stable.</td><td>To increase platelet count monitoring for safety purposes</td></tr>
<tr><td>Section 8.6.3 Stopping Rules for Platelet Count Results</td><td>Administration of steroids is recommended for patients whose platelet count is less than 25,000/mm^3. Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (**note**: may require continuation with oral steroids after methylprednisolone).</td><td>To provide added patient safety regarding platelet count reductions and treatment recommendations</td></tr>
<tr><td>Section 8.6.3 Stopping Rules for Platelet Count Results</td><td>Table 2 Actions in Patients with Low Platelet Count
<table>
<tr><th>Platelet Count on Rx</th><th>Drug Dose</th><th>Monitoring</th></tr>
<tr><td>Normal range, > 140K/mm^3</td><td>No action</td><td>Monitor every 2 weeks</td></tr>
<tr><td>100K-140K/mm^3</td><td>No action</td><td>Closer observation
Monitor every one week</td></tr>
<tr><td>75K-100K/mm^3</td><td>Reduce dose frequency to 300mg every 2 weeks or reduce dose to 150 mg weekly</td><td>Closer observation
Monitor every one week</td></tr>
<tr><td>50K-75K/mm^3</td><td>Dose pause
When platelet count returns to > 100K/mm^3 restart dosing at dose frequency of 300 mg every 2 weeks or 150 mg weekly only if approved by Sponsor Medical Monitor</td><td>Closer observation
Monitor every 2-3 days until 2 successive values show improvement
Consider discontinuation of antiplatelet agents/NSAIDS/anticoagulant medication</td></tr>
<tr><td>25K-50K/mm^3</td><td>If occurs while on dose of 300 mg every 2 weeks or 150 mg every week then permanently discontinue Study Drug, otherwise dose pause.
When platelet count returns to > 100K/mm^3 restart dosing at dose frequency of 300 mg every 2 weeks or 150 mg weekly only if approved by Sponsor Medical Monitor</td><td>Closer observation
Monitor daily until 2 successive values show improvement then monitor every 2-3 days until platelet count stable
Discontinue antiplatelet agents/NSAIDS/anticoagulant medication while platelet count < 50K/mm^3 if possible</td></tr>
</table></td><td>To provide added patient safety regarding platelet count reductions, ISIS 304801 dose exposure, and treatment recommendations</td></tr>
</table>

<table>
<tr><th>Protocol Section</th><th>Description of Change</th><th>Rationale</th></tr>
<tr><td>Section 8.6.3 Stopping Rules for Platelet Count Results Continued</td><td>Table 2 Actions in Patients with Low Platelet Count Continued
<table>
<tr><td>< 25K/mm^3</td><td>Permanently discontinue Study Drug</td><td>Closer observation:
Monitor daily until 2 successive values show improvement then monitor every 2-3 days until platelet count stable.
Steroids recommended*
Consider need for hospitalization and referral to hematologist
Discontinue antiplatelet agents/NSAIDS/anticoagulant medication while platelet count < 50K/mm^3 if possible</td></tr>
</table>
* Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (note: may require continuation with oral steroids after methylprednisolone)</td><td></td></tr>
<tr><td>Section 8.1 Volanesorsen Administration</td><td>Patients entering this ISIS 304801-CS7 study on a reduced dose or dose frequency of Study Drug (volanesorsen), for safety or tolerability reasons in their index study (ISIS 304801-CS6 or –CS16), will receive a reduced dose or dose frequency of volanesorsen for continued safety or tolerability as outlined in Sections 8.5 and 8.6. Patients entering this CS7 study having dose or dose frequency reduced in the CS16 index study after 13 weeks of treatment, as outlined in CS16 Amendment 4 Section 8.7, can receive the 300 mg once weekly dose of volanesorsen.</td><td>To allow patients to receive a suitable dose or dose frequency of volanesorsen, based on safety/ tolerability or non-safety/ tolerability dosing rules</td></tr>
</table>

PROTOCOL SYNOPSIS

Protocol Title	An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Study Phase	3
Indication	Familial Chylomicronemia Syndrome
Study Objectives	To evaluate the safety and efficacy of extended dosing with volanesorsen (volanesorsen sodium 300 mg) in patients with FCS
Study Design	This is a multi-center, open-label extension study of ISIS 304801-CS6 and ISIS 304801-CS16. All patients will receive volanesorsen 300 mg once per week for 52 weeks. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period. Following the Week 52 visit, patients will enter a 13-week post-treatment evaluation period.
Number of Patients	Up to approximately 70 patients dosed
Study Population	Inclusion Criteria: 1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law 2. Age ≥ 18 years at time of informed consent 3. Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement. Patients who are enrolled in ISIS 304801-CS16 must also meet the following criteria in order to enter into the Extension Study: a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L) b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) by documentation of at least 1 of the following: • Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1) • Post heparin plasma LPL activity of ≤ 20% of normal c. Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 study 4. Able and willing to participate in a 65-week study 5. Satisfy 1 of the following: a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved), abstinent*, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration

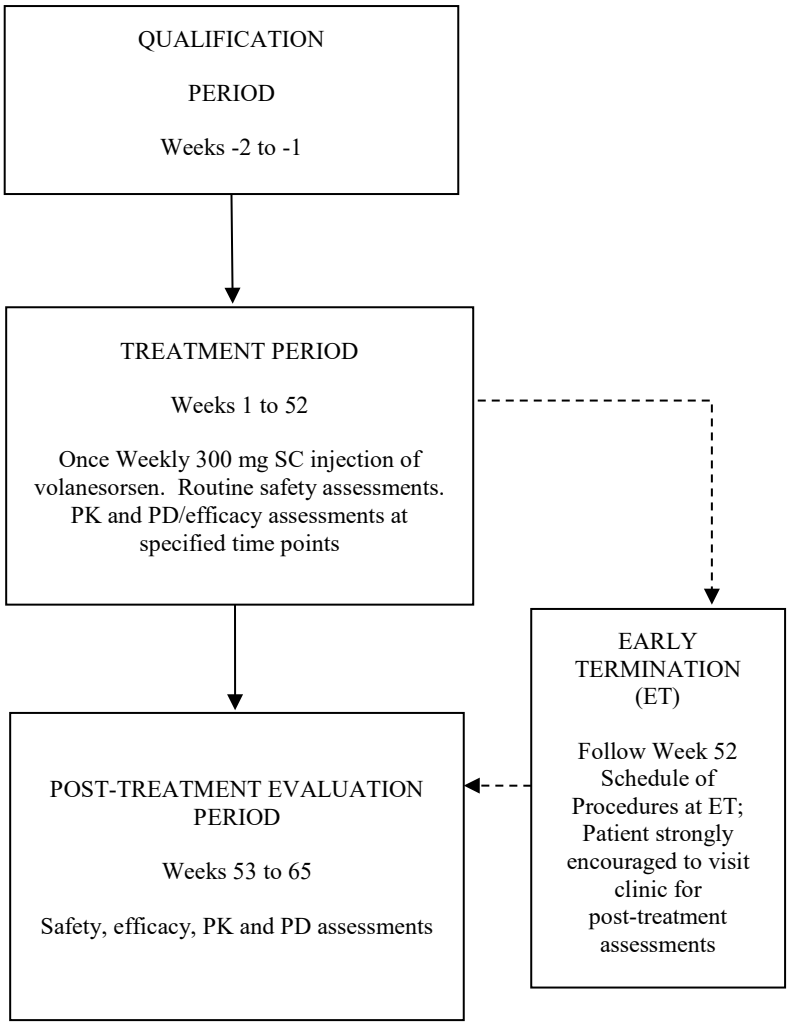
PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	Inclusion Criteria: *Continued* b. Males: Surgically sterile, abstinent* or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration * Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception Exclusion Criteria: 1. Have any new condition or worsening of existing condition which in the opinion of the Investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study 2. Unwilling to comply with lifestyle requirements for the duration of the study (Section 6.3)
Treatment Group	Volanesorsen 300 mg once per week
Study Drug Administration	Volanesorsen will be administered as subcutaneous (SC) injections.
Dose Adjustments	Dose adjustments, including dose interruptions and/or decreasing the dose frequency will be allowed for safety or tolerability after consultation with the Sponsor Medical Monitor.
Rationale for Dose and Schedule Selection	The dose of 300 mg once weekly was chosen for the double-blinded placebo-controlled Phase 3 index studies (ISIS 304801-CS6- and ISIS 304801-CS16) based on the pharmacodynamic and safety analysis of the Phase 2 studies which included a subset of patients with FCS. This is an extension to the ISIS 304801-CS6 and ISIS 304801-CS16 index studies. Only the subset of patients from ISIS 304801-CS16 with FCS diagnosis may enter the Extension Study. (Please refer to inclusion criteria #3, above)
Study Visit Schedule and Procedures	The study for an individual patient will generally consist of the following periods: • A qualification period of up to 2 weeks (unless approved by the Sponsor). Please refer to Section 4.1 and Appendix A. A 52-week treatment period during which volanesorsen will be administered as a once weekly SC injection • A 13-week post-treatment evaluation period The patients, Investigators, study staff, and the Sponsor will remain blinded to lipid data through the last patient's Week 13 visit of the extension study or until results from the database locks for the ISIS 304801-CS6 and ISIS 304801-CS16 index studies becomes available, whichever comes first. Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), adverse events (AE), concomitant medication/procedure information, lipid panel, volanesorsen plasma concentrations, immunogenicity (IM) testing, liver/spleen magnetic resonance imaging (MRI), ECGs, echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Dietary counseling will be repeated at intervals throughout the treatment and follow-up period and a daily food/drink diary will be completed for the week prior to each quarterly visit by each patient. Following the Week 52 visit, patients will enter the 13-week post-treatment evaluation period.

PROTOCOL SYNOPSIS *Continued*

Safety and Tolerability Evaluations	Overall safety and tolerability of volanesorsen will be assessed by determining the incidence and severity of adverse and serious adverse events (including independently adjudicated events of acute pancreatitis and MACE), withdrawals due to adverse events, and changes in laboratory and other safety parameters.
Planned Analyses	Safety Endpoints: • Adverse events including adjudicated events of acute pancreatitis and MACE • Vital signs and weight • Physical examinations • Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis) • Echocardiography • Electrocardiograms (ECGs) • Use of concomitant medications • MRIs Efficacy Endpoints: • Percent change and absolute change from baseline in fasting TG • Frequency and severity of patient reported abdominal pain during the treatment period • Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-high-density lipoprotein-cholesterol (non-HDL-C), apolipoprotein B [apoB], high-density lipoprotein-cholesterol (HDL-C), apolipoprotein A-1 [apoA-1], very-low-density lipoprotein-cholesterol (VLDL-C), and LDL-C • Percent change from baseline in fasting total apolipoprotein C-III (apoC-III) • Quality of Life questionnaires (EQ-5D, SF-36) • Adjudicated acute pancreatitis event rate • Other symptoms: eruptive xanthoma, lipemia retinalis
Pharmacokinetic Evaluations	Plasma samples will be taken from all patients for the measurement of volanesorsen as follows: trough levels (pre-dose) throughout treatment and post-treatment levels during the post-treatment follow-up period. In a subset of patients, more frequent assessment of plasma concentrations of volanesorsen will be performed to determine volanesorsen pharmacokinetic parameters. Plasma sample collection time points are detailed in Appendix A and Appendix C.
Statistical Considerations	No sample size calculations were performed as this is an extension study to the double-blind placebo controlled ISIS 304801-CS6 and ISIS 304801-CS16 index studies.
Sponsor	Ionis Pharmaceuticals, Inc.
Collaborator	Akcea Therapeutics

STUDY DESIGN AND TREATMENT SCHEMA



STUDY GLOSSARY

Abbreviation/Acronym	Definition
ADA	anti-drug antibody
AE	adverse Event
ALP	alkaline Phosphatase
ALT	alanine Aminotransferase
ANA	antinuclear Antibody
apoA-1	apolipoprotein A-1
apoB	apolipoprotein B
apoC-III	apolipoprotein C-III
apoE	apolipoprotein E
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
CBC	complete blood count
C_{max}	maximum observed drug concentration
CRF	case report form
DNA	deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
ET	early termination
FAS	full analysis set
FCS	Familial Chylomicronemia Syndrome
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
GPIHBP1	Glycosylphosphatidylinositol-anchored HDL-binding Protein 1
HAPI	Heritability and Phenotype Intervention
HbA1c	Glycated Hemoglobin
HDL	High-Density Lipoprotein
HDL-C	High-Density Lipoprotein-Cholesterol
hsCRP	High-sensitivity C-reactive protein
ICH	International Conference on Harmonization
IDL	Intermediate density lipoprotein
IEC	Independent Ethics Committee
IM	immunogenicity
Index Studies	ISIS 304801-CS6 and ISIS 304801-CS16

INR	International Normalized Ratio
IRB	Institutional Review Board
IXRS	Interactive Voice/Web-Response System
LDL	Low-Density Lipoprotein
LDL-C	Low-Density Lipoprotein-Cholesterol
LMF1	Lipase Maturation Factor 1
LPL	Lipoprotein Lipase
MACE	Major Acute Cardiovascular Event
MOE	2′-*O*-(2-methoxyethyl)
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NCS	not clinically-significant
NOAEL	No-Observed-Adverse-Effect Level
non-HDL-C	Non-High-Density Lipoprotein-Cholesterol
OLE	Open Label Extension
OTC	over the counter
PFS	prefilled syringe
PD	pharmacodynamic
PK	pharmacokinetic
PPS	per protocol set
PT	prothrombin time
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SUSAR	suspected unexpected serious adverse reaction
T2DM	type 2 diabetes mellitus
T_{max}	time to maximal concentration
TG	triglycerides
Treatment-emergent	occurring after first dose of Study Drug
TRL	Triglyceride-Rich Lipoproteins
ULN	upper limit of normal
VLDL	Very-Low-Density Lipoprotein
VLDL-C	Very-Low-Density Lipoprotein-Cholesterol
VLDL-TG	Lipoprotein-Triglyceride
WMA	World Medical Association

1. OBJECTIVES

The objective of the study is to evaluate the safety and efficacy of extended dosing with volanesorsen in patients with familial chylomicronemia syndrome.

2. BACKGROUND AND RATIONALE

2.1 Overview of Disease

Familial Chylomicronemia Syndrome (FCS) is an inherited disease characterized by severe hypertriglyceridemia and chylomicronemia, and risk or history of pancreatitis. It is a rare autosomal recessive disease that can be diagnosed either in childhood or adulthood.

Fasting plasma triglyceride (TG) levels in FCS patients are typically 10-fold to 100-fold above normal (1,500 to 15,000 mg/dL), despite extreme dietary fat restriction (20 g or approximately 15-20% of daily calorie intake) (Brunzell 1999-2011). Patients with FCS often present in infancy or childhood with frequent and severe abdominal pain, repetitive colicky pain, repeated episodes of potentially fatal acute pancreatitis, and failure to thrive (Brunzell 1999-2011; Tremblay et al. 2011). Physical examination frequently reveals eruptive xanthomas, lipemia retinalis and hepatosplenomegaly, and plasma from patients appears lactescent, interfering with determination of other laboratory parameters (Tremblay et al. 2011).

Patients with fasting triglyceride levels > 10 mmol/L probably have a component of chylomicronemia. Clinical diagnosis would include evidence of clinical features of chylomicronemia syndrome and secondary causes such as uncontrolled type 1 or type 2 diabetes mellitus (T2DM), hypothyroidism, poor diet, alcohol use, nephrotic syndrome or use of associated medications should be ruled out. The diagnosis of FCS may be made more specifically by genotyping or confirmation of very low or absent lipoprotein lipase (LPL) enzyme activity in post heparin plasma (Brunzell 1999-2011).

Patients with FCS carry a heavy burden of medical complications, the most serious, as described above, being an extreme risk of recurrent and potentially fatal pancreatitis. Due to the recurrent episodes of acute pancreatitis, these patients may also develop chronic pancreatitis and signs of exocrine or endocrine pancreatic insufficiency, including diabetes mellitus (Gaudet et al. 2013). While the pathophysiology underlying chylomicron-related pancreatitis has not been completely elucidated, 1 hypothesis is that large chylomicrons lodged in pancreatic capillaries are exposed to pancreatic lipase, with the subsequent release of free fatty acids through the hydrolysis of chylomicron-associated TGs. High concentrations of free fatty acids are thought to damage pancreatic cells leading to emergent pancreatitis (Yang et al. 2009; Berglund et al. 2012).

The etiology of extreme hypertriglyceridemia in FCS is considered to be ineffective triglyceride clearance, due to an extremely low level of LPL activity. LPL normally functions to hydrolyze triglycerides (TG) in chylomicrons along the luminal surface of capillaries, mainly in heart, skeletal muscle, and adipose tissue, promoting triglyceride clearance from the circulation. LPL is regulated by a number of key genes, and loss-of-function mutations in one of these genes, or the LPL gene itself, results in FCS (Surendran et al. 2012). In addition to loss of function mutations, null mutations, and nonsense mutations in the LPL gene, other genes currently identified in FCS patients, and known to directly influence LPL activity include: apolipoprotein C-II (APOC2) a cofactor for LPL (Schuster et al. 2011); apolipoprotein A-V

(APOA5) an enhancer of LPL activity (Schaap et al. 2004); lipase maturation Factor 1 (LMF1), a transmembrane protein involved in LPL maturation (Doolittle et al. 2009); glycosylphosphatidylinositol-anchored HDL-binding protein 1 (GPIHBP1), a capillary endothelial cell protein that provides a platform for LPL-mediated processing of chylomicrons (Beigneux et al. 2007).

2.2 Therapeutic Rationale

Apolipoprotein C-III (ApoC-III), a key regulator of plasma triglyceride levels, is a 79 amino acid glycoprotein synthesized principally in the liver (Ooi et al. 2008; Figure 1). ApoC-III is a major regulator of lipoprotein metabolism and plays a pivotal role in regulating plasma TG levels (Chan et al. 2008). It is a component of triglyceride-rich lipoproteins (TRLs) and a potent inhibitor of LPL (Lemieux et al. 2003). At higher concentrations apoC-III also inhibits hepatic lipase activity (Kinnunen and Ehnolm 1976), an enzyme which plays an important role in the conversion of dense very-low-density lipoprotein (VLDL) to intermediate density lipoprotein (IDL) and to LDL (Mendivil et al. 2010), as well as in the remodeling of HDL (Brown et al. 2010). In addition, increased apoC-III content adversely affects apoE-mediated hepatic uptake of TG-rich remnants (Mann et al. 1997). Thus, elevated plasma apoC-III levels are associated with impaired hydrolysis and retarded clearance of TG-rich particles, resulting in the accumulation of lipoprotein-triglyceride (VLDL-TG) and chylomicrons in plasma and the development of hypertriglyceridemia (Ito et al. 1990).

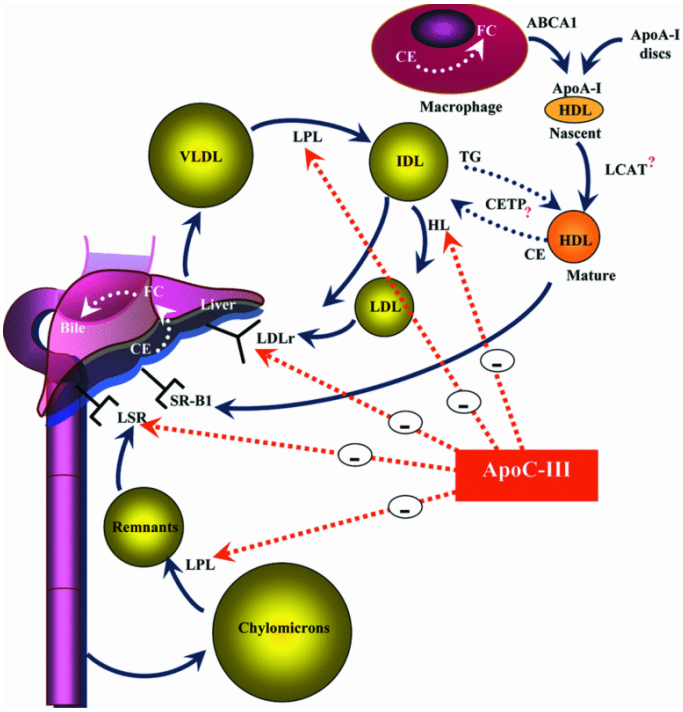


Figure 1 ApoC-III Regulates Lipoprotein Metabolism by Multiple Mechanisms

From Ooi et al. 2008; ABCA1 = ATP-binding cassette A1, apo = apolipoprotein, CE = cholesterol ester, CETP = cholesterol ester transfer protein, FC = free cholesterol, HDL = high-density lipoprotein, HL = hepatic lipase, IDL = intermediate-density lipoprotein, LCAT = lecithin cholesterol acyltransferase, LDL = low-density lipoprotein, LDLr = LDL receptor, LPL = lipoprotein lipase, LSR = lipolysis-stimulated receptor, SR-B1 = scavenger receptor B-1, TG = triglyceride, VLDL = very low-density lipoprotein.

Mechanistically, FCS is primarily a consequence of ineffective clearance of TRL. ApoC-III is a prominent component of TRL (e.g., VLDL and chylomicrons). In addition to its role in inhibiting LPL, apoC-III inhibits TRL remnant (TG-depleted remnant lipoprotein) uptake by hepatic lipoprotein receptors by steric inhibition of the interaction of apoE with these receptors.

Human genetic data have demonstrated positive phenotypic associations with loss (e.g., null or nonsense mutations) and negative effects with gain of function mutations (Atzmon et al. 2006; Pollin et al. 2008; Petersen et al. 2010). A novel nonsense mutation in the apoC-III gene was identified in the heritability and phenotype intervention (HAPI) heart study in Old Order Amish that results in lower plasma apoC-III and TG levels and lower LDL-C, increased HDL-C and reduced atherosclerosis (Pollin et al. 2008). In another study involving a group of 214 Ashkenazi Jews of advanced age (had passed or nearly reached 100 years of age), genotype analysis revealed a polymorphism in the apoC-III gene (APOC3-641CC genotype) with a clear pattern of age-dependent frequency that was associated with significantly lower levels of apoC-III protein, a favorable lipoprotein profile and increased longevity (Atzmon et al. 2006). In contrast to the Amish and Ashkenazi apoC-III polymorphisms associated with lower plasma TG, apoC-III polymorphisms associated with higher plasma TG have also been recently described (Petersen et al. 2010). In a cohort of lean (mean body mass index [BMI] = 24.7 ± 3.6 kg/m^2) Asian Indians, carriers of apoC-III variant alleles (C-482T, T-455C, or both) were noted to have significantly higher plasma apoC-III and TG levels, and decreased ability to clear postprandial plasma TG from the circulation. Taken together, the available data strongly support the development of a therapy that reduces plasma apoC-III levels in order to reduce the very high circulating triglyceride and chylomicron levels that are accompanied by increasing risk for acute pancreatitis.

Given the profound reductions in TGs observed with volanesorsen treatment in FCS patients who have no detectable LPL activity (See Section 2.3.4), and the mechanistic data available to date on apoC-III function, potential mechanisms that explain how apoC-III inhibition results in triglyceride reduction in FCS patients include: (1) enhancing the very small residual amounts of LPL activity that these patients may have, below the limit of detection of the assay in many cases (2) potentially enhanced activity of other lipases also involved in the metabolism and breakdown of TGs, such as hepatic lipase or endothelial lipase (Kinnunen and Ehnolm 1976), and (3) apoC-III interaction with Apolipoprotein E (apoE), an important factor in liver reuptake of lipid particles by blocking apoE-mediated uptake of lipid particles in the liver (Breyer et al. 1999), and therefore, reducing apoC-III might enhance apoE-mediated uptake of lipid particles. Volanesorsen-mediated reduction of apoC-III could be contributing to one or all of these mechanisms resulting in the observed potent and sustained reductions in TG.

Through a novel apoC-III lowering mechanism of action, volanesorsen may provide the potential to manage triglyceride levels in FCS patients.

2.3 Volanesorsen

2.3.1 Mechanism of Action

Volanesorsen is a second-generation antisense oligonucleotide (ASO) drug targeted to human apoC-III. It is complementary to a region within the 3′ untranslated region of the apoC-III messenger ribonucleic acid (mRNA) and binds to the mRNA by Watson and Crick base pairing.

The hybridization (binding) of volanesorsen to the cognate mRNA, results in the RNase H1-mediated degradation of the apoC-III mRNA, thus preventing production of the apoC-III protein. Maximal antisense-mediated reduction of target mRNA levels is typically greater than 90% of control levels in sensitive tissues (Crooke and Bennett 1996; Zhang et al. 2010). Furthermore, reduction in target mRNA levels using this approach correlates directly with a subsequent reduction in target protein levels.

2.3.2 Chemistry

Chemically, volanesorsen is a synthetic oligomer of 20 nucleotides (i.e., a 20-mer) that are connected sequentially by phosphorothioate linkages. The nucleotide sequence of volanesorsen (Figure 2) is complementary to a 20-nucleotide stretch within the 3′ untranslated region of the apoC-III mRNA transcript at base position 489-508. Structurally, the oligonucleotide has 3 regions. Two (2) of them, the 5 nucleotides at the 5′ end and the 5 nucleotides at the 3′ end, are composed of 2′-*O*-(2-methoxyethyl) (MOE)-modified ribonucleotides. These MOE-modified nucleotides confer (1) increased affinity to the target mRNA (Altmann et al. 1996; McKay et al. 1999), (2) increased resistance to exonucleases and endonucleases (thereby increasing stability in tissue) (Geary et al. 2003), and (3) amelioration of some of the high dose toxicities thereby resulting in an improved safety profile compared to first generation antisense drugs containing phosphorothioate modified oligodeoxynucleotides (DNA) (Henry et al. 2000). The third region, the central portion of the oligonucleotide, is composed of 10 oligodeoxynucleotides. This chimeric design is called a MOE-Gapmer, and volanesorsen employs this chimeric structure to enable use of the RNase H1-mechanism for antisense activity. This is because while the 2′-MOE modification confers increased stability and affinity, it does not support RNase H1 catalysis of RNA hybridized to 2′-MOE-modified nucleotides (McKay et al. 1999). This is caused by conformational changes induced in the heteroduplex by 2′-alkoxy:RNA hybrids that are not recognized by RNase H1 enzymes (Inoue et al. 1987; Monia et al. 1993). By limiting the 2′-MOE modification to nucleotides flanking the phosphorothioate oligodeoxynucleotide core, the beneficial attributes of the 2′-MOE chemistry are preserved while also retaining RNase H1 recognition.

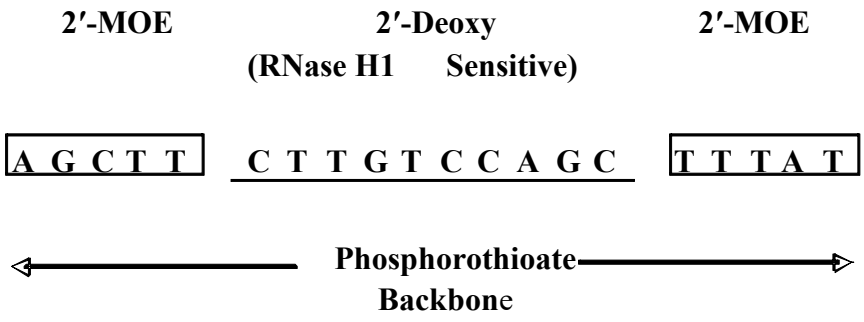


Figure 2 Design of Chimeric 2′-MOE Phosphorothioate Oligonucleotides (MOE-Gapmer). The sequence of volanesorsen is shown

2.3.3 Preclinical Experience

Inhibition of apoC-III using volanesorsen has been shown to potently reduce hepatic apoC-III mRNA as well as plasma apoC-III protein and TG in a dose- and time-dependent fashion in several species, including human apoC-III transgenic mice, and other rodent and monkey models. Treatment with volanesorsen also resulted in reduced VLDL and chylomicron TG and reduced postprandial TG in hypertriglyceridemic monkeys (Graham et al. 2013).

The pharmacokinetics (PK) and toxicity of volanesorsen have been assessed in mice, rats, and cynomolgus monkeys. General toxicity studies with volanesorsen for up to 39 weeks of treatment followed by up to a 20-week recovery period are complete. The preclinical toxicology program for volanesorsen consists of single dose safety pharmacology studies in the monkey (cardiovascular) and mouse (neurobehavioral and pulmonary assessment studies), *in vitro* and *in vivo* genetic toxicity assessment, repeat dose fertility and/or developmental reproductive toxicology studies in the mouse and rabbit and evaluation in the *in vitro* human Ether-á-go-go-related gene (hERG) assay.

Volanesorsen treatment-related findings in mice and monkeys were generally consistent with those expected for the 2′-MOE-class of ASOs. Treatment-related findings included effects consistent with drug accumulation in tissues in rodents and monkeys, species-dependent proinflammatory response in rodents and monkeys and complement activation and reductions in platelet counts in the monkey. In the mouse and monkey general toxicity studies, reduction of hepatic apoC-III mRNA (> 75%) was not associated with any findings that could be considered related to the pharmacologic inhibition of apoC-III for up to 39 weeks of treatment.

The long-term, chronic toxicology studies in rodents with volanesorsen produced a significant proinflammatory response that led to subsequent effects on the heart at high doses. The rodent species are most sensitive to the proinflammatory effects of antisense molecules. Importantly, these effects on the heart were not observed in the monkey chronic toxicity studies even at the highest doses tested where drug exposure was higher than that in rodents.

Because these changes were not observed in monkeys, the findings in the heart are considered to be rodent-specific and not relevant to humans. Nevertheless, such effects will be monitored by measurement of echocardiograms that will be included in this clinical study.

Volanesorsen caused no untoward effects in safety pharmacology studies (*in vitro* and *in vivo*) and was non-genotoxic (*in vitro* and *in vivo*). Volanesorsen had no effects on fertility or embryo/fetal development in the mouse or rabbit reproductive toxicity studies. In these studies, volanesorsen was detected in placental tissue but not in fetal tissue indicating that little, if any, drug was able to cross the placenta to reach the fetus. Reduction of apoC-III mRNA (64% in males and 47% in females) also did not affect fertility or cause untoward effects on embryo/fetal development in mice.

Detailed information concerning the preclinical studies conducted with volanesorsen can be found in the volanesorsen Investigator's Brochure.

2.3.4 Clinical Experience

Detailed information concerning the clinical studies conducted with volanesorsen can be found in the volanesorsen Investigator's Brochure. A summary is included below.

Volanesorsen has been evaluated in one Phase 1 study and two Phase 2 studies, all double blinded and placebo controlled. The total exposures comprise 99 patients and healthy volunteers administered volanesorsen from 50 to 400 mg subcutaneously up to 3 months (compared to 37 administered placebo).

All clinical trials of volanesorsen have shown large and clinically meaningful reductions in fasting plasma apoC-III and TG (~80% and 70%, respectively, mean reduction from baseline with 300 mg dose) with a very high degree of consistency of response between the different patient groups. This includes healthy volunteers, patients with moderate to severe hypertriglyceridemia not on background TG-lowering therapy, patients with moderate to severe hypertriglyceridemia on a background stable fibrate therapy (Gaudet et al. 2015), patients with FCS, and patients with T2DM.

In a Phase 2 study, 3 patients with FCS were treated with 300 mg/wk volanesorsen in an open label fashion. These patients had a mean baseline fasting TG level of 1,844 mg/dL and all 3 patients achieved TG levels below or close to 500 mg/dL during the dosing period out to Day 92 (Figure 3). Two (2) of the FCS patients had an absolute reduction in fasting TG in excess of 1,500 mg/dL (Gaudet et al. 2014).

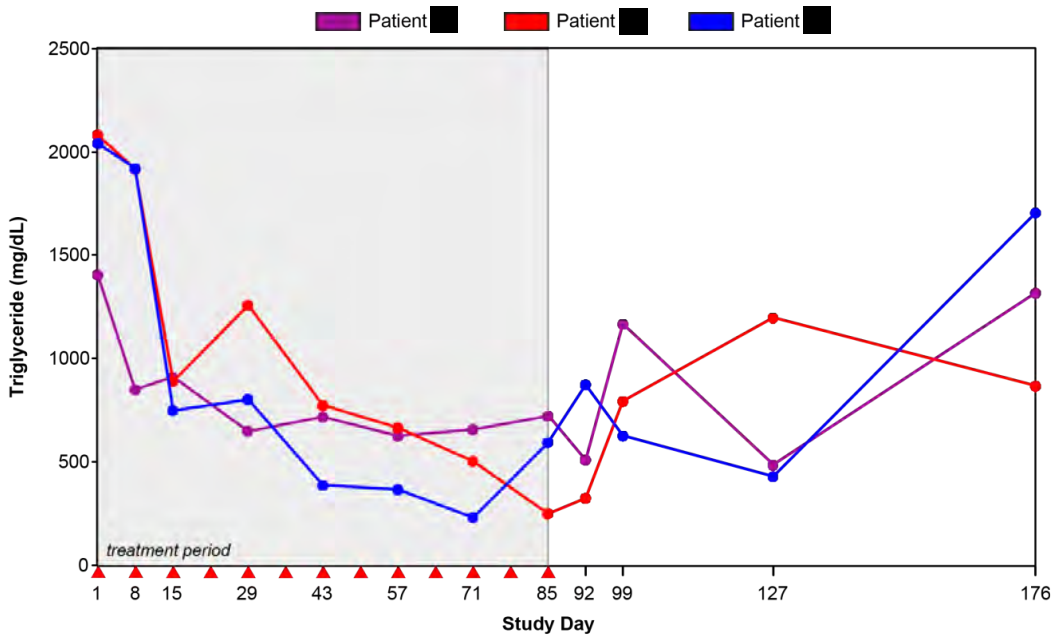


Figure 3 Fasting Triglycerides in Patients with FCS Treated with Volanesorsen

In clinical studies conducted to date volanesorsen has been well-tolerated and has shown a favorable safety profile. There has been no clinical or laboratory evidence of drug-drug interactions.

In the completed studies there have been no volanesorsen associated laboratory abnormalities suggestive of an effect on the renal (serum creatinine, proteinuria) or hepatic systems (alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin). In Phase 2 studies, there was a mild decrease of platelet count associated with volanesorsen administration that recovered in the post-treatment period and was not associated with platelet-related adverse events (AEs). In the blinded ongoing clinical trials of ISIS 304801, 2 patients of 142 dosed (as of February 29, 2016) had a decrease in platelet count to less than 50,000/mm^3 in the absence of major bleeding or clinically-relevant non-major bleeding and had Study Drug paused as per the monitoring and stopping rules for platelet counts (Section 8.6.3). Platelet counts recovered following suspension of dosing.

The most frequently observed AEs with volanesorsen were local reactions at the injection site. Local cutaneous reactions at the injection site defined as those events presenting as either pain, tenderness, erythema, pruritus or swelling occurring on the day of injection and persisting for at least 2 days were infrequent (~15% of injections), were almost always mild, resolved spontaneously, were non-progressive, and were not associated with systemic sequelae.

2.4 Rationale for Dose and Schedule of Administration

The dose and schedule selected for this study is 300 mg per week for 52 weeks. The dose of 300 mg per week is supported by both the cumulative nonclinical data available to date and the Phase 2 clinical data. In nonclinical studies, volanesorsen treatment-related effects in rodents and monkeys were consistent with drug accumulation in tissues and also include species-specific proinflammatory responses. In the monkey, the No-Observed-Adverse-Effect Level (NOAEL) was defined by the cumulative clinical pathology results and histopathology data which provide an adequate clinical margin. No nonclinical findings were considered to be related to the pharmacologic inhibition of apoC-III.

The safety data to date suggest that volanesorsen has been well-tolerated at dose levels up to 300 mg in patients with high triglycerides (including type 2 diabetes patients and administration in combination with fibrates and statins) with the most common AEs being local to the injection site and predominantly mild. A pooled analysis of safety for the Phase 2 studies did not demonstrate any clear difference in safety or tolerability between the different doses tested (100 mg, 200 mg, and 300 mg per week for 13 weeks).

Analysis of the cohorts in which volanesorsen was studied at different doses demonstrates dose-dependent pharmacology with respect to pharmacodynamic (PD) effect on the target, apoC-III, with a clear difference in the TG-lowering effect between the different doses in the 100 mg to 300 mg dose range as compared to placebo.

In addition to the nonclinical and clinical experience of volanesorsen, the dose and schedule of administration is supported by the preclinical and clinical safety experience of several other 2′-MOE-modified ASOs that have been safely administered intravenously and subcutaneously in multiple clinical studies at doses up to 1000 mg and for treatment durations that exceed 24 months (Santos et al. 2015).

3. EXPERIMENTAL PLAN

3.1 Study Design

This is an open-label extension to the Phase 3 study of volanesorsen in patients with FCS (ISIS 304801-CS6 or ISIS 304801-CS16). Up to approximately 70 patients will receive 300 mg once weekly volanesorsen for 52 weeks.

Following the Week 52 visit, patients enter a 13-week post-treatment evaluation period.

3.2 Number of Study Centers

This study will be conducted at multiple centers worldwide.

3.3 Number of Patients

Up to approximately 70 patients will be dosed.

3.4 Overall Study Duration and Follow-up

The Study will consist of the following periods:

- A qualification period of up to 2 weeks (unless approved by the Sponsor). Please refer to Section 4.1 and Appendix A.
- A 52-week treatment period during which volanesorsen will be administered as a once weekly SC injection
- A 13-week post-treatment evaluation period

Please refer to the Schedule of Procedures in Appendix A.

3.4.1 Qualification

A period of up to 2 weeks is given to complete qualification assessments outlined in the Schedule of Procedures (Appendix A).

3.4.2 Treatment

The treatment period is 52 weeks. Eligible patients will report to the Study Center for assessments at specified intervals throughout the 52-week treatment period as detailed in the Schedule or Procedures (Appendix A). During the treatment period, volanesorsen is administered by SC injection once weekly.

3.4.3 Post-Treatment

The post-treatment evaluation period is 13 weeks and consists of 2 Study Center visits on Weeks 58 and 65.

3.5 End of Study

The End-of-Study is last patient, last visit.

3.6 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will review (as needed) safety, tolerability and efficacy data collected on volanesorsen during this study. Based on its ongoing assessment of the safety and tolerability of volanesorsen, the DSMB will provide recommendations to the Sponsor for modifying, stopping or continuing the study as planned. Details on the safety assessments, frequency of review and meeting schedules are outlined in the DSMB Charter and/or the statistical analysis plan (SAP).

4. PATIENT ENROLLMENT

4.1 Qualification

Before patients may be enrolled into the study, the Sponsor requires a copy of the Study Center's written independent ethics committee/institutional review board (IEC/IRB) approval of the protocol, informed consent form, and all other patient information.

Patients or their legally acceptable representatives must sign the consent form before any study-specific procedures or evaluations related to this open label study are performed. During the qualification period, the eligibility of the patient to continue in the extension study will be determined. Final assessments from the ISIS 304801-CS6 or ISIS 304801-CS16 studies may be used for qualification. A period of up to 2 weeks after completion of the ISIS 304801-CS6 or ISIS 304801-CS16 index studies (unless approved by the Sponsor) is given to complete qualification. Qualified patients will retain the unique patient identification number that was assigned to them during the ISIS 304801-CS6 or ISIS 304801-CS16 index studies. The patient identification number will be used to identify the patient throughout the extension trial and must be used on all study documentation related to that patient. The patient identification number must remain constant throughout the extension trial.

4.2 Enrollment

Patients will be enrolled after all qualification assessments have been completed and after the Investigator has verified that they are eligible per criteria in Sections 5.1 and 5.2. No patient may begin treatment prior to enrollment.

Eligible patients will be enrolled using an Interactive Voice/Web-Response System (IXRS).

5. PATIENT ELIGIBILITY

To be eligible to participate in this study candidates must meet the following eligibility criteria within 2 weeks of Study Day 1, or at the time point specified in the individual eligibility criterion listed.

5.1 Inclusion Criteria

1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law
2. Age ≥ 18 years at time of informed consent
3. Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement. Patients who are

enrolled in ISIS 304801-CS16 must also meet the following criteria in order to enter into the Extension Study:

a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L)

b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) by documentation of at least 1 of the following:

- Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1)
- Post heparin plasma LPL activity of ≤ 20% of normal

c. Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 study.

4. Able and willing to participate in a 65-week study

5. Satisfy 1 of the following:

a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved), abstinent*, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration.

b. Males: Surgically sterile, abstinent* or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration.

* Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception

5.2 Exclusion Criteria

1. Have any new condition or worsening of existing condition which in the opinion of the Investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study.

2. Unwilling to comply with lifestyle requirements for the duration of the study (Section 6.3).

6. STUDY PROCEDURES

6.1 Study Schedule

All required study procedures are outlined in Appendices A, B, C, and D.

6.1.1 Qualification

Please refer to Section 4.1 and Appendix A.

6.1.2 Treatment Period

The patients, Investigators, study staff, and the Sponsor will remain blinded to lipid data through the last patient's Week 13 visit of the extension study or until results from the database locks for the ISIS 304801-CS6 and ISIS 304801-CS16 index studies become available, whichever comes first.

During the treatment period, patients will report to the study center for clinic visits a minimum of 5 times during Weeks 1-52 (see Schedule of Procedures in Appendix A). Study Drug will be administered once weekly (Section 8.1). Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), AEs, concomitant medication/procedure information, lipid panel, volanesorsen plasma concentrations, immunogenicity (IM) testing, liver/spleen MRI, ECGs, echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Adverse events at the injection site should be collected as adverse events. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period and all patients will complete a daily food diary for one week prior to their quarterly visit. All blood and urine samples should be collected prior to volanesorsen administration. Blood sampling at Weeks 2.5, 4, 6, 8, 10, 12, 15, 17, 19, 21, 23, 25, 28, 30, 32, 34, 36, 40, 42, 44, 46, 48, 50, 54, 56, and 58 may be conducted by a home healthcare nurse. Approval for study procedures to be conducted by a home healthcare nurse on other outpatient visit days will require prior approval by the Sponsor. Patients must be fasted prior to drawing all blood samples and samples drawn locally should also be sent to the central laboratory for analysis whenever possible. Every effort should be made to ensure the previous week's dose is given 7 days prior to a scheduled clinic visit. Dosing instructions and training will be provided to the patient where applicable.

All reasonable attempts should be made to ensure compliance with the visit schedule as outlined in Appendix A. However, in the event that a visit does not occur or is delayed, all subsequent visits should be calculated based on the time elapsed since Day 1 rather than from the date of the previous visit.

6.1.3 Pharmacokinetic (PK) Subgroup

A subgroup of patients will participate in an extended PK collection. Patients in this subgroup will have more frequent PK sampling over a 24-hour period following the first dose on Study Day 1 in order to evaluate the plasma PK parameters of volanesorsen. Patients in this subgroup will have an additional visit to the clinic, or by a home healthcare nurse, on Day 2 to collect a 24-hour post-dose blood draw after dosing on Day 1. The detailed PK sampling schedules are outlined in Appendix C.

Participation in the PK subgroup is optional for sites and patients, and consent may be withdrawn for the subgroup-specific procedures (e.g., multiple blood draws for PK) without being withdrawn from the study. If a patient withdraws consent from the subgroup procedures, he/she should remain on study and continue to follow all the non-subgroup assessments and procedures as outlined in Appendix A.

6.1.4 Post-Treatment Period

After completion of the Week 52 visit assessments, patients will enter the 13-week post-treatment evaluation period. This period consists of 4 Study Center visits on Weeks 54, 56, 58 and 65 as outlined in the Schedule of Procedures in Appendix A.

6.2 Additional Study Assessments

6.2.1 Laboratory Assessments

Laboratory analyte samples will be collected throughout the study. A list of these analytes is contained in Appendix B.

Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1-week and determined not to have met a stopping rule before dosing can continue.

If there is no reportable platelet count within 14 days of the last platelet count, the Investigator will contact the patient to hold dosing until a new platelet count is obtained and reviewed.

All platelet count results will be promptly reviewed by the Investigator to ensure that the count has not met the stopping rule and to determine whether the rate of decline is suggestive that the patient could be approaching the dose pause rule of 75,000/mm^3.

Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor.

6.2.2 Physical Exams and Vital Signs

Physical exams and vital signs will be performed as indicated in the Schedule of Procedures (Appendix A). Vital signs should include weight, blood pressure, pulse rate, respiratory rate and body temperature. Blood pressure and pulse rate will be recorded after the patient has been in a sitting position for at least 5 minutes. Semi-supine systolic and diastolic blood pressure should always be measured on the same arm (preferentially on the left arm). Height will be measured at the Day 1 visit.

6.2.2.1 Eruptive Xanthoma

At each visit, patients will be asked whether they have had any episodes of eruptive xanthoma since their last visit and the number/duration of the events will be recorded. Physical exams should also include skin examination for presence/resolution of eruptive xanthomas. If a patient experiences an episode of eruptive xanthoma during the study, photos of the area should be taken, if possible.

6.2.2.2 Lipemia Retinalis

If possible, lipemia retinalis will be assessed by fundus photography prior to administration of the first dose of Study Drug (for ISIS 304801-CS16 rollover patients) and repeated at Week 52. Images will be evaluated by an independent assessor, blinded to the patient's treatment assignment.

6.2.3 Echocardiography

Echocardiography for assessment of left and right ventricular function and mitral and aortic valve function will be conducted at Week 26 and Week 52 in all patients. For the purpose of assessment of treatment-emergent changes, all echocardiograms will be evaluated on an ongoing basis by an independent central reader. Results will be provided to the DSMB for their review.

6.2.4 ECG

The ECG will be recorded after the patient has been resting in a supine position for at least 5 minutes. ECGs will be performed in triplicate at Week 13, Week 26, Week 38, Week 52, and Week 65.

6.2.5 MRI

MRI of the liver and spleen will be conducted at Week 52 for all patients for whom MRI is not contraindicated, e.g., patients having metal implants.

MRIs will be conducted using standardized procedures and settings. MRIs will be read by an independent central reader to assess liver fat and liver and spleen size**.**

6.2.6 Quality of Life Assessments

All patients will complete Quality of Life Questionnaires (EQ-5D and SF-36) at Week 1, Week 13, Week 26, Week 52, and Week 65.

6.2.7 Disease Symptom Diary

All patients will complete a symptom questionnaire once a week starting at the beginning of the qualification period and continuing to the end of the post-treatment follow-up period.

6.2.8 Diet Monitoring

The diets of patients enrolled in the study will be monitored as follows:

1. All patients will be required to maintain a 7-day food diary prior to Week 1, Week 13, Week 26, Week 52, and Week 65.

2. Patients will receive diet/alcohol counseling by qualified study personnel at clinic visits throughout the course of the study. Qualified study personnel will telephone the patient to provide diet/alcohol counseling for visits that are conducted by a clinical service.

3. In addition to the 7-day food diary and the diet /alcohol counseling during clinic visits, telephone calls from a dietitian or qualified study personnel to assess as to how each patient is maintaining their diet will be conducted randomly during the treatment and post treatment follow-up periods.

6.2.9 Family History

Family history of hypertriglyceridemia and pancreatitis will be collected for each patient.

6.2.10 Lipoprotein Lipase Activity Sample Collection

Lipoprotein lipase (LPL) activity will be measured in ISIS 304801-CS16 rollover patients if needed for study qualification. In brief, fasted patients will be given a low intravenous dose of heparin. A blood sample will be drawn prior to and at 10 or 15 minutes after the heparin administration for measurement of LPL activity as per instructions provided to the Investigator.

6.3 Restriction on the Lifestyle of Patients

6.3.1 Contraception Requirements

All male patients and women of childbearing potential must refrain from sperm/egg donation and either be abstinent* or, if engaged in sexual relations of child-bearing potential, practice effective contraception from the time of signing the informed consent form until at least 13 weeks after their last dose of study treatment.

Male patients must also encourage their female partner to use effective contraception from the time of signing the informed consent until 13 weeks after the subject's last dose of study treatment.

For the purposes of this Study, women of childbearing potential are defined as any female who has experienced menarche, and who does not meet 1 of the following conditions:

- Postmenopausal: 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved
- 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Post hysterectomy

For the purposes of the study, effective contraception is defined as follows:

For male patients:

- Effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the use of condoms together with spermicidal foam/gel/film/ cream/suppository. Male patients must also encourage their female partner to use effective contraception from the time of signing the informed consent until 3 months after the patient's last dose of study treatment. Effective contraceptive for the female partner includes: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or barrier methods (female condom*, diaphragm, sponge, cervical cap) together with spermicidal foam/gel/film/cream/suppository. Male patients with partners that are pregnant must use condoms to ensure that the fetus is not exposed to the Study Drug.

For female patients:

- Using one or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or any 2 barrier methods (a combination of male or female condom* with diaphragm, sponge, or cervical cap) together with spermicidal foam/gel/film/cream/suppository.

*Note: A female condom and a male condom should not be used together as friction between the two can result in either product failing.

* Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception

6.3.2 Other Requirements

All patients will be required to fast for at least 10 hours and preferably not more than 12 hours before visits requiring fasted blood sampling.

All patients will be encouraged to follow a diet comprising ≤ 20 g fat per day during the study.

Alcohol should not be consumed during the study.

All patients will be given an instruction card that must be presented to the treating physician if a suspected case of pancreatitis occurs. The card will explain that the patient is in a clinical trial and that serum lipase and/or amylase measures should be done in order to adjudicate the event, based on Atlanta Classification (Banks et al. 2013). If serum or amylase activity is less than 3 x upper limit of normal (ULN), imaging, preferably contrast-enhanced computed tomography, should be considered to confirm the diagnosis of acute pancreatitis per the Atlanta Criteria.

7. STUDY DRUG

7.1 Volanesorsen Description

Volanesorsen drug product (ISIS 304801) characteristics are listed in Table 1.

Volanesorsen (ISIS 304801) is contained in glass prefilled syringes (PFS). Volanesorsen and its storage and preparation instructions will be provided by the Sponsor or designee. Volanesorsen must be stored securely at 2° to 8° C and be protected from light.

Table 1 Volanesorsen (ISIS 304801) Characteristics

Strength	200 mg/mL
Volume/Formulation	1.5 mL solution per PFS
Dose	300 mg once weekly
Route of Administration	SC

7.2 Packaging and Labeling

The Sponsor will provide the Investigator with packaged volanesorsen labeled (ISIS 304801) in accordance with specific country regulatory requirements.

7.3 Study Drug Accountability

The study staff is required to document the receipt, dispensing, and return/destruction of volanesorsen provided by the Sponsor. The Study Center must return all unused volanesorsen to the Sponsor or designee. All used syringes must be disposed of as per the site's hazardous waste destruction policy.

8. TREATMENT OF PATIENTS

8.1 Volanesorsen Administration

For each individual patient, volanesorsen will be administered subcutaneously as a single 1.5 mL 300 mg injection once weekly for Weeks 1-52. Patients entering this ISIS 304801-CS7 study on a reduced dose or dose frequency of Study Drug (volanesorsen), for safety or tolerability reasons in their index study (ISIS 304801-CS6 or –CS16), will receive a reduced dose or dose frequency of volanesorsen for continued safety or tolerability as outlined in Sections 8.5 and 8.6. Patients entering this CS7 study having dose or dose frequency reduced in the CS16 index study after 13 weeks of treatment, as outlined in CS16 Amendment 4 Section 8.7, can receive the 300 mg once weekly dose of volanesorsen.

Patients should receive 1 dose per week, with weeks always defined relative to Study Day 1. For example if a patient receives the first dose on a Monday, subsequent doses should be given on Mondays, if possible. If a patient misses an injection, or if dosing on the usual day is not possible, the patient can reschedule the injection provided that 2 doses are administered at least 2 days apart.

Every effort should be made to ensure the previous week's dose is given 7 days prior to a scheduled clinic visit.

Please refer to the Study Drug Manual provided by the Sponsor for more detailed instructions for volanesorsen preparation and administration.

8.2 Other Protocol-Required Drugs

There are no other protocol-required drugs (Section 6.2.5).

8.3 Other Protocol-Required Treatment Procedures

There are no other protocol required treatment procedures for this study.

8.4 Treatment Precautions

There are no specific treatment precautions required for this study.

8.5 Safety Monitoring Rules

Please refer also to the 'Guidance for Investigator' section of the Investigator's Brochure.

For the purposes of safety monitoring baseline is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 (e.g., qualification assessments or assessments from the final visits of ISIS 304801-CS6 and ISIS 304801-CS16 index studies if used for qualification).

In addition to the standard monitoring of clinical safety parameters, the following guidelines are provided for the monitoring of selected parameters chosen based on preclinical and clinical observations.

Confirmation Guidance: At any time during the study (Treatment or Post-Treatment Periods), the initial clinical laboratory results meeting the safety monitoring or stopping criteria presented below **must be confirmed** by performing measurements (ideally in the same laboratory that performed the initial measurement) on new specimens. All new specimen collections should take place as soon as possible (ideally within 3 days of the initial collection). For stopping rules, if the initial laboratory result is observed during the Treatment Period, the results from the retest **must be available** prior to administering the next dose of volanesorsen.

In addition to the safety monitoring parameters listed below, the Sponsor may request confirmation of additional lab values.

Re-dosing Guidance: Patients with initial laboratory test values that reach a stopping rule must not be re-dosed until the re-test results are available. In general, patients who do not meet the stopping rules based upon retest may continue dosing. However, the Investigator and the Sponsor Medical Monitor (or appropriately qualified designee) should confer as to whether additional close monitoring of the patient is appropriate. Reduction in dose or dose frequency may also be initiated as noted in Section 8.7. If any of the stopping criteria described below (refer to Sections 8.6.1 to 8.6.3) are met, the patient will be dose paused or permanently discontinued (as described in the stopping criterion concerned) from further treatment with volanesorsen, and evaluated fully as outlined below and in consultation with the Sponsor Medical Monitor or appropriately qualified designee, and will be followed up in accordance with Section 8.8 of the protocol.

8.5.1 Safety Monitoring for Liver Chemistry Tests

The following rules are adapted from the draft guidance for industry, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," issued by the U.S. Department of Health and Human Services, Food and Drug Administration, July 2009. For a definition of Baseline please refer to guidance in Section 8.5 above.

In the event of an ALT or AST measurement that is > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) at any time during the study (Treatment or Post-Treatment Period), the initial measurement(s) should be confirmed as described above. Additional confirmatory measurements should also be performed if ALT or AST levels increase to 5 x ULN.

Frequency of Repeat Measurements: Patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) should have their liver chemistry tests (ALT, AST, alkaline phosphatase (ALP), international normalized ratio

(INR) and total bilirubin) retested at least once-weekly until ALT and AST levels become ≤ 1.2 x ULN or 1.2 x baseline value if the baseline value was > ULN.

Further Investigation into Liver Chemistry Elevations: For patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), the following evaluations should be performed:

1. Obtain a more detailed history of symptoms and prior and concurrent diseases
2. Obtain further history for concomitant drug use (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
3. Obtain a history for exposure to environmental chemical agents and travel
4. Serology for viral hepatitis (HAV IgM, HBsAg, HCV antibody, CMV IgM, and EBV antibody panel)
5. Serology for autoimmune hepatitis (e.g., antinuclear antibody [ANA])

Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic CT or MRI scans, may be performed at the discretion of the Investigator, in consultation with the Sponsor Medical Monitor. Repetition of the above evaluations should be considered if a patient's ALT and/or AST levels reach 5 x ULN.

8.5.2 Safety Monitoring for Platelet Count Results

Actions to be taken in the event of reduced platelet count are shown in Table 2 in Section 8.6.3.

Additional lab tests will be determined by the Sponsor Medical Monitor or designee in consultation with the Investigator.

Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor (See also Stopping Rules Section 8.6.3).

8.5.3 Safety Monitoring for Minor Bleeding Events

Minor bleeding events are those that do not fulfill the criteria for major bleeding or clinically-relevant, non-major bleeding events (which are defined in Section 8.6.3), for example excess bruising, petechiae, gingival bleeding on brushing teeth. If a minor bleeding event occurs, the Investigator must notify the Sponsor Medical Monitor and additional testing of coagulation parameters activated partial thromboplastin time (aPTT), prothrombin time (PT), INR and platelet count should be performed.

8.5.4 Safety Monitoring for Constitutional Symptoms

Patients will be instructed to promptly report any signs of symptoms of fever or constitutional symptoms that may arise during the study and the Investigator should closely evaluate all potential causes, including concomitant illness. Patients that experience persistent constitutional symptoms should be discussed with the Sponsor Medical Monitor or designee to determine whether additional monitoring or laboratory tests are required.

8.5.5 Safety Monitoring for LDL-C Elevations

Beginning at Week 13, laboratory alerts will be in place to notify the Investigator if a patient has a low-density lipoprotein-cholesterol (LDL-C) > 160 mg/dL (> 130 mg/dL for patients with T2DM) on 2 consecutive visits. If this occurs, LDL-C values for this patient will be unblinded for the remainder of the study and the Investigator will be encouraged to initiate/adjust treatment to lower LDL-C according to country-specific guidelines (e.g., initiate statin therapy or increase the statin dose for patients who are already on treatment).

8.5.6 Safety Monitoring for Insulin, Oral Antidiabetic Medication and Glucose

All patients on insulin will monitor their glucose levels with a glucometer as per standard practice guidelines and bring their glucometer or glucometer log printout to every clinic visit. In addition, patients who are not on insulin but use a glucometer should also bring their glucometer and/or glucometer log printout to every clinic visit.

- The Investigator or delegate will review the glucometer reading or printout at every clinic visit to evaluate if fasting pre-breakfast self-monitored plasma glucose values exceed threshold values as per the Safety Monitoring Rules for Hyperglycemia below.

All diabetic patients will note any changes in their insulin dose and /or oral antidiabetic therapy, as well as any hypoglycemic episode they may experience.

- The Investigator or delegate will ask patients at every clinic visit if they made changes in their insulin dose or oral antidiabetic therapy, and if they experienced a hypoglycemic episode.
  - Patients will be instructed on the monitoring and management of hypoglycemic episodes at each visit.
  - Documented symptomatic hypoglycemic episodes should be captured as adverse events in the adverse event CRF. Documented symptomatic hypoglycemia is defined as typical hypoglycemia symptoms accompanied by measured plasma glucose ≤ 70 mg/dL (≤ 3.9 mmol/L).
  - Any changes in insulin dose or oral antidiabetic therapy should be captured into the Concomitant Medication CRF.

8.5.7 Safety Monitoring for Documented Severe Hypoglycemia

A **documented severe hypoglycemic event** is defined as 1 in which the patient requires assistance of another person to obtain treatment for the event and has a plasma glucose level ≤ 70 mg/dL (≤ 3.9 mmol/L). The rescue treatment of hypoglycemia may include IV glucose or buccal or intramuscular glucagon.

The definition of severe symptomatic hypoglycemia includes all episodes in which neurological impairment was severe enough to prevent self-treatment and which were thus thought to place patients at risk for injury to themselves or others. Note that "requires assistance" means that the patient could not help himself or herself. Someone being kind that assists spontaneously the patient when not necessary does not qualify as "requires assistance."

Severe hypoglycemia will be qualified as a SAE only if it fulfills SAE criteria.

If a patient presents with symptoms of hypoglycemia, the Investigator will need to take immediate action to confirm the patient's glucose level and treat the patient accordingly.

The experience of hypoglycemia may vary greatly from patient to patient. However, there are certain classical signs and symptoms, of which patients should be aware as a clue that their blood glucose may be low. Common symptoms include headache, heart pounding, confusion, disorientation, numbness or tingling, pale skin, shakiness or tremulousness, increased appetite, anxiousness or nervousness, lightheadedness or dizziness, sweating, and weakness. Coma could occur if blood sugar correction is not performed.

If patients suspect they might be having a hypoglycemia reaction, they should check their blood glucose using their meters as soon as possible, before treatment if possible, provided they feel it is safe to do so. If there is doubt about safety they should treat the event first, using some sugar, milk, or juice for example, then obtain and record a blood glucose value as soon as possible thereafter. The time and nature of treatment should be noted, and especially if any blood glucose result was before or after treatment. It would be helpful for the patient to note if a contributory factor (e.g., missed or reduced meals, unaccustomed physical activity) occurred earlier in the day of the event.

8.5.8 Safety Monitoring for Hyperglycemia

Upward dose titration and/or addition of any other anti-hyperglycemic agent(s) will not be allowed during the course of the study, unless specific threshold values are met at Week 13 or later and confirmed on subsequent testing (ideally within 1 week of the initial test).

HbA1c is monitored every 3 months throughout the study. In addition, patients on insulin should self-monitor their plasma glucose (SMPG) routinely on a glucometer as per practice guidelines. If a fasting pre-breakfast SMPG value exceeds the specific glycemic limit, the patient should check it again on the following 2 days. If all the fasting pre-breakfast values on 3 consecutive days exceed the specific limit, the patient should contact the Investigator and an unscheduled central laboratory FPG measurement and HbA1c should be performed.

The threshold values are defined as:

- FPG > 270 mg/dL (15.0 mmol/L)
- HbA1c > 9% (for patients with baseline HbA1c < 8% and HbA1c increase of more than 1% from baseline (for patients with baseline HbA1c ≥ 8 and < 9%)

In case of confirmed FPG/HbA1c above the threshold value, the Investigator should ensure that no reasonable explanation exists for insufficient glucose control and in particular that:

- Plasma glucose was actually measured in the fasting condition (i.e., after at least 10 hours fast)
- Absence of intercurrent disease which may jeopardize glycemic control. In case of an emergency (e.g., surgery, infection), the Investigator can take appropriate measures for glycemic control
- Compliance to treatment is appropriate

- Compliance to diet and lifestyle is appropriate

If any of the above can reasonably explain the insufficient glycemic control, the Investigator should consider the following:

- Investigation and treatment of intercurrent disease (to be reported in adverse event (AE)/concomitant medication parts of the e-CRF)
- Stress on the absolute need to be compliant to treatment
- Organize a specific interview with a Registered Dietician or other qualified nutrition professional and stress on the absolute need to be compliant to diet and lifestyle recommendations

A FPG/HbA1c follow-up assessment should be arranged after appropriate action has been taken. If none from the above-mentioned reasons can be found, or if appropriate action fails to decrease FPG/HbA1c under the threshold values, additional medication may be introduced at the Investigator's discretion and according to local guidelines after discussion with the Sponsor Medical Monitor.

8.5.9 Acute Pancreatitis

If a patient has an episode of acute pancreatitis, dosing with Study Drug should be suspended temporarily until the patient is clinically stable. The suitability of the patient for continued dosing and the need for any modification to treatment schedule (refer to Section 8.7) will be determined by the Investigator in consultation with the Study Medical Monitor.

8.6 Stopping Rules

For the purposes of stopping rules baseline is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1.

8.6.1 Stopping Rules for Liver Chemistry Elevations

In the event of laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor,** dosing of a patient with volanesorsen will be stopped permanently; values that are not confirmed due to failure to retest or missing lab values will be presumed confirmed:

1. ALT or AST > 8 x ULN, which is confirmed
2. ALT or AST > 5 x ULN, which is confirmed and persists for ≥ 2 weeks
3. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed **and** total bilirubin > 2 x ULN or INR > 1.5
4. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed, and the new appearance (i.e., onset coincides with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> ULN) felt by the Investigator to be potentially related to hepatic inflammation

8.6.2 Stopping Rules for Renal Function Test Results

In the event of a persistent elevation that is observed over 2 consecutive weeks, for any of the 3 criteria below, dosing of a patient with volanesorsen may be stopped temporarily:

1. Serum creatinine increase that fulfill all of the following criteria: ≥ 0.3 mg/dL (26.5 µmol/L) and ≥ 40% above baseline creatinine values and > ULN
2. Proteinuria, dipstick 2 + (confirmed by dipstick retest and then further confirmed by a quantitative total urine protein measurement of > 1.0 g/24-hour)
3. Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault ≤ 40 mL/min that is confirmed by a 24-hour urine collection

The possible dosing re-initiation or follow-up schedule for any events meeting either of these criteria will be determined by the Investigator **in consultation with** the Sponsor Medical Monitor or designee.

8.6.3 Stopping Rules for Platelet Count Results

Actions to be taken in the event of a low platelet count are summarized in Table 2 below.

In the event of a platelet count less than 75,000/mm^3 that is associated with major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with volanesorsen will be stopped permanently. The follow-up schedule for any events meeting this stopping criterion will be determined by the Investigator in consultation with the Sponsor Medical Monitor.

In the event of any platelet count less than 25,000/mm^3, or a platelet count less than 50,000/mm^3 that occurs while the patient is on dosing at 300 mg every 2 weeks or 150 mg every week then dosing of a patient with volanesorsen will be stopped permanently. Platelet count will be monitored daily until 2 successive values show improvement then monitored every 2-3 days until platelet count is stable.

Administration of steroids is recommended for patients whose platelet count is less than 25,000/mm^3. Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (**note:** may require continuation with oral steroids after methylprednisolone).

In the event of a platelet count less than 75,000/mm^3, and in the absence of major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with volanesorsen should be suspended temporarily until the platelet count has recovered to ≥ 100,000/mm^3. If dosing is continued it should be at a reduced dose frequency of 300 mg every 2 weeks or a reduced dose of 150 mg per week (refer to Section 8.7). The suitability of the patient for continued dosing will be determined by the Investigator in consultation with the Study Medical Monitor and will be based on factors such as the original rate of decline in the patient's platelet count, whether any bleeding events were experienced by the patient, and the speed of recovery of platelet count upon holding of dosing.

If after the first dosing rechallenge the platelet count again falls below 75,000/mm^3, then dosing of the patient must be held until the platelet count again returns to at least 100,000/mm^3. The suitability of the patient for continued dosing and the need for any further modification to treatment schedule or dose (refer to Section 8.7) will be re-examined by the Investigator in consultation with the Study Medical Monitor based on (at least) the factors mentioned above.

If after the second rechallenge the platelet count falls below 75,000/mm^3 and is subsequently confirmed (see Section 8.5), dosing with volanesorsen will be stopped permanently. The follow-up schedule for any events meeting this stopping criterion will be determined by the Investigator in consultation with the Study Medical Monitor.

Following a rechallenge platelet count should be tested every week until count is stable.

Any unreportable platelet count result must be rechecked and determined not to have met a stopping rule before dosing can continue.

If there is no reportable platelet count within 14 days of the last platelet count, the Investigator will contact the patient to hold dosing until a new platelet count is obtained and reviewed.

Definition of Major Bleeding Events (Schulman et al. 2005):

- Fatal bleeding, and/or
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarterial or pericardial, or intramuscular with compartment syndrome, and/or
- Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more within 24 hours, or leading to transfusion of 2 or more units of whole or red cells

Definition of Clinically-Relevant, Non-Major Bleeding Events (Schulman et al. 2005):

1. Multiple-source bleeding
2. Spontaneous hematoma > 25 cm^2
3. Excessive wound hematoma (not injection site related)
4. Macroscopic hematuria (spontaneous or lasting > 24 hours if associated with an intervention)
5. Spontaneous rectal bleeding; epitasis, gingival bleeding, hemoptysis, hematemesis
6. Bleeding after venipuncture for > 5 minutes

Table 2 Actions in Patients with Low Platelet Count

Platelet Count on Rx	Drug Dose	Monitoring
Normal range, > 140K/mm^3	No action	Monitor every 2 weeks
100K-140K/mm^3	No action	Closer observation Monitor every one week
75K-100K/mm^3	Reduce dose frequency to 300 mg every 2 weeks or reduce dose to 150 mg weekly	Closer observation Monitor every one week
50K-75K/mm^3	Dose pause When platelet count returns to >100K/mm^3 restart dosing at dose frequency of 300 mg every 2 weeks or 150 mg weekly **only if approved by Sponsor Medical Monitor**	Closer observation Monitor every 2-3 days until 2 successive values show improvement Consider discontinuation of antiplatelet agents/NSAIDS/ anticoagulant medication
25K-50K/mm^3	If occurs while on dose of 300 mg every 2 weeks or 150 mg every week then permanently discontinue Study Drug, otherwise dose pause. When platelet count returns to > 100K/mm^3 restart dosing at dose frequency of 300 mg every 2 weeks or 150 mg weekly **only if approved by Sponsor Medical Monitor**	Closer observation Monitor daily until 2 successive values show improvement then monitor every 2-3 days until platelet count stable Discontinue antiplatelet agents/NSAIDS/anticoagulant medication while platelet count < 50K/mm^3 if possible
< 25K/mm^3	Permanently discontinue Study Drug	Closer observation: Monitor daily until two successive values show improvement then monitor every 2-3 days until platelet count stable Steroids recommended* Consider need for hospitalization and referral to hematologist Discontinue antiplatelet agents/NSAIDS/anticoagulant medication while platelet count < 50K/mm^3 if possible

* Recovery in platelet count may be accelerated by administration of high dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (**note:** may require continuation with oral steroids after methyl prednisolone)

8.7 Adjustment of Dose Frequency

Dose adjustments for platelet count reduction must be made in accordance with Section 8.6.3 and Table 2 (above).

Other dose adjustments, including dose interruptions, and/or decreasing the dose or dose frequency will be allowed for safety and tolerability. Any proposed adjustment to treatment schedule must be discussed with, and approved by, the Study Medical Monitor prior to initiation. Up to 2 adjustments in the treatment schedule may be allowed.

Patients may be dose paused in response to AEs after consultation with Study Medical Monitor.

8.8 Discontinuation of Study Treatment

A patient must permanently discontinue study treatment for any of the following:

- The patient becomes pregnant. Report the pregnancy according to instructions in Section 9.5.4
- The patient withdraws consent
- The patient experiences an AE that necessitates permanent discontinuation of study treatment
- The patient develops laboratory test abnormalities that meet any of the stopping rules listed in Section 8.6

The reason for discontinuation of study treatment must be recorded in the CRF and source documentation.

8.8.1 Follow-up Visits for Early Termination from Treatment Period

Any patient who discontinues early from the Treatment Period should be strongly encouraged to attend applicable landmark visits at Weeks 12, 13, 25, 26, and 51, 52 (calculated based on the time elapsed since Day 1) to collect fasting lipid panels and conduct safety assessments in accordance with the schedule of procedures in Appendix A. Any patient who discontinues treatment after Week 44 should also be strongly encouraged to attend a final follow-up visit (Week 65 visit assessments) approximately 13 weeks after their last dose of Study Drug, in addition to the applicable landmark visits.

If the patient declines or is unable to participate in the above, an early termination (ET) visit (Week 52 visit assessments) should be performed at the time of withdrawal, at a minimum, and ideally within 2 weeks from the last dose of Study Drug.

8.8.2 Follow-up Visits for Early Termination from Post-Treatment Follow-up Period

The patient who requests to withdraw from the study during the Post-Treatment Follow-up Period should be encouraged to undergo a final follow-up visit (Week 65, see Appendix A) prior to leaving the study.

If a patient withdraws due to an AE at any time during the study, the Investigator should arrange for the patient to have appropriate follow-up until the AE has resolved or stabilized.

8.9 Withdrawal of Patients from the Study

Patients must be withdrawn from the study for any of the following:

- Withdrawal of consent
- The patient is unwilling or unable to comply with the protocol

Other reasons for withdrawal of patients from the study might include:

- At the discretion of the Investigator for medical reasons

- At the discretion of the Investigator or Sponsor for noncompliance
- Significant protocol deviation

All efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information, including the reason for withdrawal from study, must be recorded in the CRF.

Any patient who withdraws consent to participate in the study will be removed from further treatment and study observation immediately upon the date of request. These patients should be encouraged to complete the ET study procedures and observations at the time of withdrawal (see Section 8.8 and Appendix A).

For patients withdrawn for reasons other than withdrawal of consent every effort should be made to complete the early termination study procedures and observations at the time of withdrawal (see Section 8.8 and Appendix A).

8.10 Concomitant Therapy and Procedures

The use of concomitant therapies or procedures defined below must be recorded on the patient's CRF. AEs related to administration of these therapies or procedures must also be documented on the appropriate CRF.

8.10.1 Concomitant Therapy

A concomitant therapy is any non-protocol specified drug or substance (including over-the-counter medications, herbal medications and vitamin supplements) administered between signing informed consent and completion of the post-treatment follow-up period. All concomitant medications/treatments and significant non-drug therapies (including supplements and assistive devices) received by a patient, including changes in the patient's current medications, must be recorded in the patient's source documents and CRF. Patients taking over the counter (OTC) omega-3 fatty acids should make every effort to remain on the same brand throughout the study.

Allowed Concomitant Therapy

Any medications deemed necessary by the Investigator are allowed except those listed in the disallowed concomitant therapy.

Disallowed Concomitant Therapy

No lipid lowering therapies (e.g., fibrates, niacin, fish oil or other products containing omega-3 fatty acids [including OTC preparations]), -glucagon-like peptide-1 (GLP-1) agonists, Glybera, or systemic corticosteroids may be started or adjusted after baseline qualification. Doses of existing oral anti-diabetic medication, oral contraceptives, hormone replacement therapy, anticoagulants, or drugs or dietary supplements with potential lipid-altering effects should not be adjusted. Study patients are prohibited from receiving other experimental agents during the study. This includes marketed agents at experimental dosages that are being tested for the treatment of hypertriglyceridemia.

Patients should consult with the Site Investigator or designee prior to initiating any new medication, including non-prescription or herbal compounds or any other non-drug therapy.

8.10.2 Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between signing of informed consent and Week 65 visit.

Disallowed Concomitant Procedure

Plasma apheresis is not allowed during the study.

8.11 Treatment Compliance

Compliance with treatment dosing is to be monitored and recorded by Study Center staff. The Study Center staff is required to document the receipt, dispensing, and return/destruction of volanesorsen. Patients that are self-administering volanesorsen at home must record treatment in a dosing diary that will be reviewed periodically by Study Center staff and the Clinical Monitor.

9. SERIOUS AND NON-SERIOUS ADVERSE EVENT REPORTING

9.1 Sponsor Review of Safety Information

Safety information will be collected, reviewed, and evaluated by the Sponsor in accordance with the Safety Management Plan throughout the conduct of the clinical trial.

9.2 Regulatory Requirements

The Sponsor is responsible for regulatory submissions and reporting to the Investigators of serious adverse events (SAEs) including suspected unexpected serious adverse reactions (SUSARs) per the International Conference on Harmonization (ICH) guidelines E2A and ICH E6. Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines.

Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) will be notified of any SAE according to applicable regulations. The Independent DSMB will be notified of any SAE as specified in the DSMB charter.

In addition to the Investigator's assessment of relatedness, the Sponsor or designee will evaluate the available information and perform an independent assessment of relatedness. While the Sponsor may upgrade an Investigator's decision it is not permissible to downgrade the Investigator's opinion for the purposes of determining whether the SAE meets the definition of a SUSAR.

The following table identifies the SAEs that the Sponsor or designee will not report on an individual basis in an expedited manner because they are anticipated to occur in the study population independent of volanesorsen exposure. The Investigator still has the responsibility to report all SAEs to the Sponsor as described in Sections 9.4.1 to 9.4.3.5.

Table 3 Expected Event for the Protocol Defined Population by Preferred Term and the Expected Incidence

Preferred Term	Expected Incidence in the Protocol Defined Population (Gaudet et al. 2010 and 2013)
Pancreatitis associated events including the PTs of hereditary pancreatitis, pancreatitis, pancreatitis acute, pancreatitis chronic, pancreatitis necrotizing, pancreatitis relapsing	0.2-0.35 events per patient-year

Fatal pancreatitis associated events will be considered as unexpected and are reportable. The Sponsor and DSMB will monitor non-fatal pancreatitis associated SAEs using the incidence rate of the event compared to the rate expected in a non-volanesorsen exposed population. If the aggregate analysis indicates that an event is occurring significantly more frequently or at a greater severity than expected, then the event will be reported.

SAEs not specified in the table will be evaluated on case by case basis to determine whether there is a reasonable possibility that the drug caused the event. If the event is considered by the Sponsor or designee to meet the definition of a SUSAR the event will be reported.

9.3 Definitions

9.3.1 Adverse Event

An adverse event is any unfavorable and unintended sign (including a clinically-significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the study or use of investigational drug product, whether or not the AE is considered related to the investigational drug product.

9.3.2 Adverse Reaction and Suspected Adverse Reaction

An adverse reaction is any adverse event caused by volanesorsen.

A suspected adverse reaction is any adverse event for which there is a reasonable possibility that volanesorsen drug caused the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

9.3.3 Serious Adverse Event (SAE)

A serious adverse event is any adverse event that in the view of either the Investigator or Sponsor, meets any of the following criteria:

- Results in death
- Is life threatening: that is, poses an immediate risk of death at the time of the event

An AE or suspected adverse reaction is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Hospitalization is defined as an admission of greater than 24 hours to a medical facility and does not always qualify as an AE
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly or birth defect in the offspring of the patient (whether the patient is male or female)
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

9.4 Monitoring and Recording Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the study (i.e., before informed consent) should be recorded as Medical History and not recorded as AEs unless the pre-existing condition worsened. The Investigator should always group signs and symptoms into a single term that constitutes a **single unifying diagnosis** if possible.

9.4.1 Serious Adverse Events

In the interest of patient safety, and in order to fulfill regulatory requirements**,** all SAEs (regardless of their relationship to volanesorsen) should be reported to the Sponsor or designee within 24 hours of the Study Center's first knowledge of the event. The collection of SAEs will begin after the patient signs the informed consent form and stop at the end of the patient's follow-up period which is defined as the Week 65 visit. When the Investigator is reporting by telephone, it is important to speak to someone in person versus leaving a message. An Initial Serious Adverse Event Form should be completed and a copy should be faxed to the Sponsor or designee.

Detailed information should be actively sought and included on Follow-Up Serious Adverse Event Forms as soon as additional information becomes available. All SAEs will be followed until resolution. SAEs that remain ongoing past the patient's last protocol-specified follow-up visit will be evaluated by the Investigator and Sponsor. If the Investigator and Sponsor agree the patient's condition is unlikely to resolve, the Investigator and Sponsor will determine the follow-up requirement.

9.4.2 Non-Serious Adverse Events

The recording of non-serious AEs will begin after the patient signs the informed consent form and will stop at the end of the patient's follow-up period, which is defined as the Week 65 visit. The Investigator will monitor each patient closely and record all observed or volunteered AEs on the Adverse Event Case Report Form.

9.4.3 Evaluation of Adverse Events (Serious and Non-Serious)

The Investigator's opinion of the following should be documented on the Adverse Event Case Report Form:

9.4.3.1 Relationship to the Study Drug

The event's relationship to volanesorsen is characterized by 1 of the following:

- **Related:** There is clear evidence that the event is related to the use of volanesorsen e.g., confirmation by positive rechallenge test
- **Possible:** The event cannot be explained by the patient's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and volanesorsen administration
- **Unlikely/Remote:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to volanesorsen administration and/or exposure suggests that a causal relationship is unlikely (For reporting purposes, Unlikely/Remote will be grouped together with Not Related)
- **Not Related:** The event can be readily explained by the patient's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and volanesorsen

9.4.3.2 Severity

The severity of AEs and SAEs will be graded based on criteria from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010 (refer to Appendix D). Any AE not listed in Appendix D will be graded as follows:

- **Mild:** The event is easily tolerated by the patient and does not affect the patient's usual daily activities
- **Moderate:** The event causes the patient more discomfort and interrupts the patient's usual daily activities
- **Severe:** The event is incapacitating and causes considerable interference with the patient's usual daily activities

If the event is an SAE, then all applicable seriousness criteria must be indicated (criteria listed in Section 9.3.3).

9.4.3.3 Action Taken with Volanesorsen

Action taken with volanesorsen due to the event is characterized by 1 of the following:

- **None:** No changes were made to volanesorsen administration and dose
- **Permanently Discontinued:** Volanesorsen was discontinued and not restarted

- **Temporarily Interrupted, restarted – same dose:** Dosing was temporarily interrupted or delayed due to the AE and restarted at the same dose
- **Reduced schedule:** Dosing frequency was reduced

9.4.3.4 Treatment Given for Adverse Event

Any treatment (e.g., medications or procedures) given for the AE should be recorded on the Adverse Event Case Report Form (treatment should also be recorded on the concomitant treatment or ancillary procedures CRF as appropriate).

9.4.3.5 Outcome of the Adverse Event

If the event is a non-serious AE then the event's outcome is characterized by 1 of the following:

- **AE Persists:** Patient terminates from the trial and the AE continues
- **Recovered:** Patient recovered completely from the AE
- **Became Serious:** The event became serious (the date that the event became serious should be recorded as the Resolution Date of that AE and the Onset Date of the corresponding SAE)
- **Change in Severity** (if applicable): AE severity changed

If the event is a SAE then the event's outcome is characterized by 1 of the following:

- **Ongoing:** SAE continuing
- **Persists (as non-serious AE):** Patient has not fully recovered but the event no longer meets serious criteria and should be captured as an AE on the non-serious AE eCRF (the SAE resolution date should be entered as the date of onset of that AE)
- **Recovered:** Patient recovered completely from the SAE (the date of recovery should be entered as the SAE resolution date)
- **Fatal:** Patient died (the date of death should be entered as the SAE resolution date)

9.4.4 Adjudication Committees

All SAEs that occur during the study that are consistent with a major acute cardiovascular event (MACE) will be adjudicated by a blinded, independent committee as outlined in the MACE Adjudication Charter.

All AEs and SAEs that occur during the study that are consistent with an event of acute pancreatitis will be adjudicated by a blinded, independent committee according to the Atlanta classification of acute pancreatitis (Banks et al. 2013) and as outlined in the Pancreatitis Adjudication Charter. In addition, data for prior episodes of acute pancreatitis or suspected pancreatitis will be collected by review of each patient's medical chart and these events will also be adjudicated.

9.5 Procedures for Handling Special Situations

9.5.1 Abnormalities of Laboratory Tests

Clinically-significant abnormal laboratory test results may, in the opinion of the Investigator, constitute or be associated with an AE. Examples of these include abnormal laboratory results that are associated with symptoms, or require treatment, e.g., bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac arrhythmias due to hyperkalemia. Whenever possible, the underlying diagnosis should be listed in preference to abnormal laboratory values as AEs. Clinically-significant abnormalities will be monitored by the Investigator until the parameter returns to its baseline value or until agreement is reached between the Investigator and Sponsor Medical Monitor. Laboratory abnormalities deemed not clinically-significant (NCS) by the Investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator should not be deemed NCS on the laboratory sheet.

The Investigator is responsible for reviewing and signing all laboratory reports. The signed clinical laboratory reports will serve as source documents and should include the Investigator's assessment of clinical significance of out of range/abnormal laboratory values.

9.5.2 Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the patient is hospitalized; the Study Center must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the patient's consent to participate in the study
- The condition that required the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the patient's consent to participate in the study and the timing of the procedure or treatment
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission

9.5.3 Dosing Errors

Volanesorsen dosing errors should be documented as Protocol Deviations. A brief description should be provided in the deviation, including whether the patient was symptomatic (list symptoms) or asymptomatic, and the event accidental or intentional.

Dosing details should be captured on the Dosing Case Report Form. If the patient takes a dose of volanesorsen that exceeds protocol specifications and the patient is symptomatic, then the symptom(s) should be documented as an AE and be reported per Section 9.4.

Should an overdose occur, the Investigator or designee should refer to the Guidance to Investigator's section of the Investigator's Brochure and contact the Sponsor or designee within 24 hours.

9.5.4 Contraception and Pregnancy

Male patients and female patients of childbearing potential must continue to use appropriate contraception with their partners, or refrain from sexual activity, as described in Section 6.3.1.

If a patient becomes pregnant or a pregnancy is suspected, or if a male patient makes or believes that he has made someone pregnant during the study, then the Study Center staff must be informed immediately. An Initial Pregnancy Form should be submitted to the Sponsor or designee **within 24 hours** of first learning of the occurrence of pregnancy. Follow-up information including delivery or termination is reported on Follow-up Pregnancy Forms and reported within 24 hours.

Payment for all aspects of obstetrical care, child or related care will be the patient's responsibility.

Female patients: If a suspected pregnancy occurs while on the study (including follow-up), a pregnancy test will be performed. The patient with a confirmed pregnancy will be immediately withdrawn from treatment with volanesorsen. However, the patient will be encouraged to complete the post-treatment follow-up portion of the study to the extent that study procedures do not interfere with the pregnancy. Regardless of continued study participation, the study physician will assist the patient in getting obstetrical care and the progress of the pregnancy will be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the Study Center and Sponsor may require access to the mother and infant's medical records for an additional 8 weeks after birth.

Male patients: The progress of the pregnancy in a male patient's partner should be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, **the Study Center and Sponsor may request access to the mother and infant's medical records for an additional 8 weeks after birth**. Follow-up will be performed to the extent permitted by applicable regulations and privacy considerations.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints

For fasting lipid measurements, the values at Month 3 analysis time point are defined as the average of Week 12 (Day 78) and Week 13 (Day 85) fasting assessments, the values of Month 6 analysis time point is at the end of Month 6 are defined as the average of Week 25 (Day 169) and Week 26 (Day 176) fasting assessments, and the values at the Month 12 analysis time point are defined as the average of Week 51 (Day 351) and Week 52 (Day 358) fasting assessments.

10.1.1 Efficacy Endpoints

- Percent change and absolute change from baseline in fasting TG
- Frequency and severity of patient reported abdominal pain during the treatment period

- Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-HDL-C, apoB, HDL-C, apolipoprotein A-1 (apoA-1), VLDL-C, and LDL-C
- Percent change from baseline in fasting total apolipoprotein C-III
- Quality of Life questionnaires (EQ-5D, SF-36)
- Adjudicated acute pancreatitis event rate
- Other symptoms: eruptive xanthoma, lipemia retinalis

10.1.2 Safety Endpoints

- Adverse events including adjudicated events of pancreatitis and MACE
- Vital signs and weight
- Physical examinations
- Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis)
- Echocardiography
- Electrocardiograms (ECGs)
- Use of concomitant medications
- MRIs

10.2 Sample Size

No sample size calculations were performed as this is an extension study to the double-blind, placebo-controlled ISIS 304801-CS6 and ISIS 304801-CS16 studies. Approximately 70 patients may be eligible to enroll into this study.

10.3 Populations

Full Analysis Set (FAS): All patients who are enrolled and have a baseline TG assessment. The FAS represents the practically-feasible intent-to-treat (ITT) population as delineated in ICH Guideline E9.

Per Protocol Set (PPS): Subset of the FAS who received 9 of first 13 scheduled doses of volanesorsen and with no significant protocol deviations that would be expected to affect efficacy and PD assessments. The detailed criteria will be specified and finalized prior to the final database lock.

Safety Set: All patients who are enrolled and receive at least 1 dose of volanesorsen.

PK Population: All patients who are enrolled, receive at least 1 dose of volanesorsen, and have at least 1 evaluable PK sample collected, analyzed, and reported.

10.4 Definition of Baseline

Definitions of baseline are given below for the purposes of the final analysis.

For fasting lipid measurements, 2 baselines are defined for each patient: ISIS 304801-CS6 or ISIS 304801-CS16 index study baseline and the baseline in this open label study, which is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 (e.g., qualification assessments or assessments from final visit of the ISIS 304801-CS6 or ISIS 304801-CS16 index studies if used for qualification).

For other measurements, baseline for patients on active treatment in the ISIS 304801-CS6 or ISIS 304801-CS16 index study will be the ISIS 304801-CS6 or ISIS 304801-CS16 index study baseline. For patients on placebo in the ISIS 304801-CS6 or ISIS 304801-CS16 index study, baseline for safety will be the last non-missing assessment prior to the first dose of Study Drug.

10.5 Interim Analysis

An interim analysis may be conducted after the last patient's Week 13 visit of the extension study or after the database of the ISIS 304801-CS6 and ISIS 304801-CS16 index studies are locked and unblinded. Both safety and efficacy information from this OLE study may be summarized during this interim analysis. Efficacy analyses will be detailed in the SAP.

10.6 Planned Methods of Analysis

All eCRF data, lab data transfers, as well as any outcomes derived from the data, will be provided in the patient data listings. Patient data listings will be presented for all patients enrolled into the study. Descriptive summary statistics including n, mean, median, standard deviation, standard error, interquartile range (25th percentile, 75th percentile), and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data by treatment group. Where appropriate, p-values will be reported. All statistical tests will be conducted using 2-sided tests with 5% Type I error rates unless otherwise stated.

All efficacy endpoints will be assessed in the FAS and PPS. All safety assessments will be performed on the Safety Set. PK endpoints will be assessed in the PK Set as applicable.

10.6.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics by treatment group. The patient disposition will be summarized by treatment group of the index studies. All patients enrolled will be included in a summary of patient disposition.

10.6.2 Safety Analysis

Treatment duration and amount of Study Drug received will be summarized by treatment group of the index studies.

Patient incidence rates of AEs will be tabulated by MedDRA system organ class, MedDRA preferred term, and treatment group of the index studies. Narratives of treatment-emergent deaths, serious and significant AEs, including early withdrawals due to AEs, will also be provided.

All treatment-emergent AEs, all treatment-emergent AEs potentially related to Study Drug, all treatment-emergent serious AEs, and all treatment-emergent serious AEs potentially related to Study Drug will be summarized.

Injection Site Reactions (ISRs) will be summarized by treatment group of the index studies, MedDRA preferred term and severity.

Independently adjudicated events of MACE and pancreatitis will be summarized by treatment group of the index studies.

Laboratory tests to ensure patient safety including chemistry panel, complete blood count (CBC) with differential, coagulation panel, IM, complement etc., will be summarized by study visits by treatment group of the index studies.

These safety variables will also be presented as change and percent change from baseline over time after Study Drug administration, as appropriate.

Vital signs, weight, ECG measures, echocardiography assessments, and MRI assessments will be tabulated by treatment group of the index studies.

10.6.3 Efficacy Analysis

Percent change and change from baseline to Month 3, Month 6, and Month 12 in fasting TG will be summarized by treatment group of the index studies. Response rate of patients with fasting plasma TG < 750 mg/dL or achieving fasting TG ≥ 40% reduction from baseline at Month 3, Month 6, and Month 12 will be summarized. Response analysis will also be conducted using a range of fasting plasma TG thresholds for determination of responder status.

Percent change and change from baseline to Month 3, Month 6, and Month 12 will also be summarized by treatment group of the index studies for other fasting lipid measures including non-HDL-C, apoB, HDL-C, apoA-1, VLDL-C, and LDL-C, total cholesterol, and fasting total apoC-III.

The incremental effects of volanesorsen on lipid measures will be explored and the association between changes in lipid parameters and total amount of drug received will be examined, as appropriate.

Frequency and severity of patient reported abdominal pain, adjudicated acute pancreatitis event rate, quality of life assessments, and comparison of other symptoms including eruptive xanthomas and lipemia retinalis will be summarized by treatment group of the index studies.

Additional details of the analyses to be conducted will be provided in the SAP.

10.6.4 Pharmacokinetic and Immunogenicity Analysis

10.6.4.1 Pharmacokinetic Analysis

For all patients, pre-dose and post-treatment volanesorsen plasma concentrations will be summarized using descriptive statistics, with stratification by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16 and IM status.

For patients in the PK subgroup only, non-compartmental PK analysis of volanesorsen will be carried out on each individual patient data set using data collected in the open label extension (OLE) study from the intensive PK subgroup, following a single dose (i.e., single-dose PK) or multiple doses (i.e., steady-state PK), depending on their earlier treatment in the index studies. On Week 1 Day 1 of the OLE study, patients who received placebo in the index study will receive the first treatment of volanesorsen (single-dose PK), while patients who received volanesorsen in the index studies had been on volanesorsen treatment for 12 months (ISIS 304801-CS6) or 6 months (ISIS 304801-CS16), thus the PK data collected from these patients reflect steady-state PK. The maximum observed drug concentration (C_{max}) and the time taken to reach C_{max} (T_{max}) will be obtained directly from the concentration-time data. Area under the plasma concentration-time curve from time zero to 24 hours ($AUC_{0\text{-}24hr}$) will be calculated using the linear trapezoidal rule. Apparent systemic (plasma) clearance after SC administration ($CL_{0\text{-}24hr}/F_{0\text{-}24hr}$) will be calculated from $CL_{0\text{-}24hr}/F_{0\text{-}24hr}$ = Actual Dose/$AUC_{0\text{-}24hr}$. Mean residence time (MRT) from time zero to 24 hours after the SC administration will be calculated from the equation, $MRT_{0\text{-}24hr} = AUMC_{0\text{-}24hr}/AUC_{0\text{-}24hr}$, where $AUMC_{0\text{-}24hr}$ is the area under the moment plasma concentration-time curve from time zero to 24 hours after the SC administration. Other PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist.

Plasma PK parameters will be summarized using descriptive statistics, with and without stratification by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16 and IM status. Additional details regarding the PK analysis will be described in the SAP.

Population PK, PK/PD, and covariate analysis may be performed if deemed appropriate, and results will be reported separately.

10.6.4.2 Immunogenicity Analysis

Immunogenicity (IM) results (screen positive/negative, confirmed positive/negative or not evaluable, and when applicable, titer of anti-volanesorsen antibodies) before, during, and after treatment with Study Drug (volanesorsen) (i.e., sample [anti-drug antibody] ADA status) will be listed by their prior treatment in study ISIS 304801-CS6 or ISIS 304801-CS16 and study day. Subject ADA status (positive/negative or not evaluable) for all evaluable patients, along with the study day associated with the first positive IM status emerged (T_{first}, i.e., onset of ADA development), the last positive IM status observed (T_{last}), the duration of ADA response (number of days between T_{first} and T_{last}) if appropriate, the last ADA sample collection day, and subject - peak titer if applicable, will be listed by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16 study day. Subjects with positive anti-volanesorsen antibody status may be further classified (when applicable) as being either ‘persistent’, ‘transient’, or ‘not determinable’, if deemed appropriate.

Additionally, the sample and subject IM incidence (number) and incidence rate (percent) will be summarized as the total number and percent of evaluated subjects with antibody negative, positive, and unknown status by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16. Furthermore, onset, duration, and titer of the ADA response, if applicable, will be summarized as median, quartiles (25% and 75%), and range.

Additional details regarding the IM data analysis will be described in the SAP.

Potential relationships between immunogenicity results (e.g., IM status) and selected efficacy (e.g., % change in fasting TG from baseline at 3-, 6-, and 12-month endpoints), safety, and PK (e.g., C_{trough}) measures will be evaluated using graphical analysis and statistical analysis. These analyses will be either conducted and included in the study report, or data pooled and analyzed from all available Phase 2 and 3 studies and reported separately.

11. INVESTIGATOR'S REGULATORY OBLIGATIONS

11.1 Informed Consent

The written informed consent document should be prepared in the language(s) of the potential patient population, based on an English version provided by the Sponsor.

Before a patient's participation in the trial, the Investigator is responsible for obtaining written informed consent from the patient after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific qualification procedures or any Study Drug are administered. The patient must be given sufficient time to consider whether to participate in the study.

The acquisition of informed consent and the patient's agreement or refusal to notify his/her primary care physician should be documented in the patient's medical records and the informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion (not necessarily an Investigator). The original signed informed consent form should be retained in the Study Master File and in any other locations required by institutional policy, and a copy of the signed consent form should be provided to the patient.

11.2 Ethical Conduct of the Study

The Guidelines of the World Medical Association (WMA) Declaration of Helsinki dated October 2002 the applicable regulations and guidelines of current Good Clinical Practice (GCP) as well as the demands of national drug and data protection laws and other applicable regulatory requirements will be strictly followed.

11.3 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent form, other written patient information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by the Sponsor before recruitment of patients into the study and shipment of volanesorsen. A copy of the written approval of any other items/materials that must be approved by the Study Center or IEC/IRB must also be received by the Sponsor before recruitment of patients into the study and shipment of Study Drug. The Investigator's Brochure must be submitted to the IEC/IRB for acknowledgement.

The Investigator must submit to and, where necessary, obtain approval from the IEC/IRB, for all subsequent protocol amendments and changes to the informed consent document. The Investigator should notify the IEC/IRB of deviations from the protocol in accordance with ICH GCP Section 4.5.2. The Investigator should also notify the IEC/IRB of serious adverse events

occurring at the Study Center and other adverse event reports received from the Sponsor, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study. Copies of the Investigator's reports, all IEC/IRB submissions and the IEC/IRB continuance of approval must be sent to the Sponsor.

11.4 Patient Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained. On the case report forms (CRF) or other documents submitted to the Sponsor, patients should be identified by unique initials and a patient study number only. Documents that are not for submission to the Sponsor (e.g., signed informed consent forms) should be kept in strict confidence by the Investigator.

In compliance with Federal and local regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the patient to permit named representatives to have access to his/her study-related records without violating the confidentiality of the patient.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments

Protocol amendments must be made only with the prior approval of the Sponsor. Agreement from the Investigator must be obtained for all protocol amendments and amendments to the informed consent document. The regulatory authority and IEC/IRB must be informed of all amendments and give approval for any amendments likely to affect the safety of the patients or the conduct of the trial. The Investigator **must** send a copy of the approval letter from the IEC/IRB to the Sponsor.

12.2 Study Termination

The Sponsor reserves the right to terminate the study according to the terms of the site contract. The Investigator reserves the right to terminate their participation in the study, according to the terms of the site contract. The Investigator/Sponsor should notify the IEC/IRB in writing of the trial's completion or early termination and send a copy of the notification to the Sponsor.

12.3 Study Documentation and Storage

An electronic case report form (eCRF) utilizing an Electronic Data Capture (EDC) application will be used for this study.

The Investigator should ensure that all appropriately qualified persons to whom he/she has delegated trial duties are recorded on a Sponsor-approved Delegation of Site Responsibilities Form.

Source documents are original documents, data, and records from which the patient's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, imaging, and correspondence. In this study, CRFs may not be used as source documents.

The Investigator and Study Center staffs are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation in accordance with Section 8 of the ICH Guidelines (E6), suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Elements should include:

- Patient files containing completed CRFs, informed consents, and supporting copies of source documentation
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation and all correspondence to and from the IEC/IRB and the Sponsor
- If volanesorsen supplies are maintained at the Study Center, proof of receipt, volanesorsen Accountability Record, Return of volanesorsen for Destruction, final study volanesorsen reconciliation, and all volanesorsen-related correspondence

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

No study document should be destroyed without prior written agreement between the Sponsor or and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor.

12.4 Study Monitoring

The Sponsor representative and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the trial (e.g., CRFs and other pertinent data) provided that patient confidentiality is respected.

The Sponsor monitor is responsible for inspecting the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to patient medical records and other study-related records needed to verify the entries on the CRFs.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's Clinical Quality Assurance Department. Inspection of Study Center facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the trial conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

To ensure the quality of clinical data a clinical data management review will be performed on patient data received by the Sponsor. During this review, patient data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or Study Center notifications will be sent to the Study Center for completion and return to Sponsor.

The Principal Investigator will sign and date the indicated places on the CRF. These signatures will indicate that the principal Investigator inspected or reviewed the data on the CRF, the data queries, and the Study Center notifications, and agrees with the content.

12.5 Language

Case report forms must be completed in English. Generic names for concomitant medications should be recorded in English if possible, unless it is a combination drug, then record the trade name in English.

All written information and other material to be used by patients and investigative staff must use vocabulary and language that are clearly understood.

12.6 Compensation for Injury

The Sponsor maintains appropriate insurance coverage for clinical trials and will follow applicable local compensation laws. Patients will be treated and/or compensated for any study-related illness/injury in accordance with the information provided in the Compensation for Injury section of the Informed Consent document.

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14. APPENDICES

Appendix A Schedule of Procedures

Appendix A Schedule of Procedures

Study Period		Qual[a]	Treatment Period																								Post Treatment Follow-up		
Study Week		-2 to -1	Wk 1		Wk 2.5	Wk 4	Wk 6	Wk 8	Wk 10	Month 3		Wk 15 & 17	Wk 19	Wk 21 & 23	Month 6		Wk 28 & 30	Wk 32	Wk 34 & 36	Wk 38	Wk 40 & 42	Wk 44	Wk 46 & 48	Month 12		Wk54 & 56	Wk 58	Wk 65
										Wk 12	Wk 13				Wk 25	Wk 26								Wk 50	Wk 52 or ET			
Study Day		-14 to -7	1	2	11	22	36	50	64	78	85	99 & 113	127	141 & 155	169	176	190 & 204	218	232 & 246	260	274 & 288	302	316 & 330	344	358	372 & 386	400	449
Visit Window+/- Days		0	0	0	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	7	7
Informed Consent		X																										
Outpatient Visit		X	X	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X	X[k]	X[k]	X[k]	X[k]	X	X[k]	X[k]	X[k]	X	X[k]	X[k]	X[k]	X[k]	X	X[k]	X[k]	X
Inclusion/Exclusion Criteria		X																										
Vital Signs + body weight (+ height on Day 1 only)		X	X			X		X			X					X				X					X			X
Physical Examination			X								X					X				X					X			X
12- lead ECG (triplicate)											X					X				X					X			X
MRI (liver/spleen)																									X[l]			
Echocardiography																X[l]									X[l]			
Blood Draw (Fasting)[c]	Chemistry Panel	X	X			X		X			X		X			X		X		X		X			X		X	X
	CBC with Differential[b]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Serum Lipid Panel	X	X			X		X		X	X				X	X				X				X	X			X
	Coagulation (aPTT, PT, INR)	PG						X			X					X				X					X			
	hsCRP, HbA1c, FPG, and de-lipidated free glycerol		X								X					X									X			X
	Sedimentation Rate		X								X					X									X			X
	Complement (C5a, Bb)		X								X					X									X			X
	Plasma PK - Volanesorsen		X[m]	X		X		X			X					X				X					X			X
	Anti-Volanesorsen Antibodies		X			X		X			X					X				X					X			X
	FSH (women only, if applicable)																											
	Serum Pregnancy Test[d]	X				X		X			X		X			X		X		X		X			X		X	X
	Archived Serum & Plasma Samples[e]		X					X			X					X									X			X

Appendix A Schedule of Procedures *Continued*

Study Period	Qual[a]	Treatment Period																								Post Treatment Follow-up		
Study Week	-2 to -1	Wk 1		Wk 2.5	Wk 4	Wk 6	Wk 8	Wk 10	Month 3		Wk 15 & 17	Wk 19	Wk 21 & 23	Month 6		Wk 28 & 30	Wk 32	Wk 34 & 36	Wk 38	Wk 40 & 42	Wk 44	Wk 46 & 48	Month 12		Wk 54 & 56	Wk 58	Wk 65
									Wk 12	Wk 13				Wk 25	Wk 26								Wk 50	Wk 52 or ET			
Study Day	-14 to -7	1	2	11	22	36	50	64	78	85	99 & 113	127	141 & 155	169	176	190 & 204	218	232 & 246	260	274 & 288	302	316 & 330	344	358	372 & 386	400	449
Visit Window+/- Days	0	0	0	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	7	7
Urinalysis[c]	X	X^n			X		X			X^n		X^n			X^n		X^n		X^n		X^n			X^n		X^n	X^n
Fundus Photography[f]	X																							X^l			
Genetic testing for FCS diagnosis (if not available in medical history)[g]	X																										
Postheparin Lipoprotein Lipase activity[h]	X																										
Weekly Study Drug: SC Injection		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Symptom Diary (weekly)	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Assessment(s)		X								X					X									X			X
Food/Drink Diary (quarterly)[i]		X								X					X									X			X
Diet/Alcohol Counseling[j]	X	X			X		X			X					X				X					X		X	X
Adverse Events	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a Qualification procedures performed (Please refer to Section 4.1)

b Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1-week and determined not to have met a stopping rule before dosing can continue. If there is no reportable platelet count within 14 days of the last platelet count, the Investigator will contact the patient to hold dosing until a new platelet count is obtained and reviewed. All platelet count results will be promptly reviewed by the Investigator to ensure that the count has not met the stopping rule and to determine whether the rate of decline is suggestive that the patient could be approaching the dose pause rule of 75,000/mm^3. Any case of a platelet count < 50,000/mm^3 should be reported in an expedited fashion to the Sponsor

Appendix A Schedule of Procedures Continued

Legend Text *Continued*

c Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours. During treatment period urine and blood samples will be collected prior to Study Drug administration. Does not apply to 24-hour PK blood draw

d Females of childbearing potential only

e Serum and plasma samples will be collected and stored for follow-up exploration of laboratory findings and/or adverse events (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.) in this or subsequent clinical studies of volanesorsen

f If possible, fundus photography should be completed prior to administration of the first dose of Study Drug (ISIS 304801-CS16 rollover patients) and repeated at Week 52 (Please refer to Section 6.2.2.2)

g Genetic testing can be conducted for study qualification (ISIS 304801-CS16 rollover patients); genetic testing will only be conducted if allowed in the geographic region and only after the patient has given specific written informed consent for genetic testing

h Post-heparin lipoprotein lipase activity can be conducted for study qualification (ISIS 304801-CS16 rollover patients; please refer to Section 6.2.10)

i In addition to diary, patients will be contacted at random times during the study to review their current eating and drinking habits

j To reinforce compliance to the diet and alcohol restrictions. Random diet/alcohol assessments (phone visits) will also be performed by dietician or study personnel

k Assessments and procedures to be conducted by either a home healthcare nurse, or the Study Center as arranged by the Study Center personnel

l A ± 7-day window is allowed for MRI, echocardiography procedures and fundus photography

m Full or abbreviated PK profile (see Appendix C)

n Expanded urinalysis (see Appendix B)

Appendix B List of Laboratory Analytes

Appendix B List of Laboratory Analytes

Based on emerging data from this or future studies, additional tests not listed below may be performed on stored samples to better characterize the profile of volanesorsen or other similar oligonucleotides.

Clinical Chemistry Panel

- Sodium
- Potassium
- Chloride
- Bicarbonate
- Total protein
- Albumin
- Calcium
- Magnesium
- Phosphorus
- Glucose
- BUN
- Creatinine
- Uric Acid
- Total bilirubin
- Direct (conjugated) bilirubin
- Indirect (unconjugated) bilirubin
- ALT
- AST
- Alkaline phosphatase

Coagulation

- aPTT (sec)
- PT (sec)
- INR

Lipid Panel

- Total Cholesterol
- LDL-C
- HDL-C
- Triglycerides
- Non-HDL-C
- VLDL-C
- apoA-1
- apoB
- apoC-III

Hematology

- Red blood cells
- Hemoglobin
- Hematocrit
- MCV, MCH, MCHC
- Platelets
- White blood cells
- WBC Differential (% and absolute)
  - Neutrophils
  - Eosinophils
  - Basophils
  - Lymphocytes
  - Monocytes

Pharmacokinetics[1] & Immunogenicity

- Volanesorsen levels in plasma
- Anti-volanesorsen antibodies in plasma

Other Assessments

- hsCRP
- Sedimentation Rate
- C5a, Bb
- De-lipidated free glycerol
- HbA1c, FPG

Urinalysis

- Color
- Appearance
- Specific gravity
- pH
- Protein
- Blood
- Ketones
- Urobilinogen
- Glucose
- Bilirubin
- Leukocyte esterase
- Nitrate
- Microscopic examination[2]

Additional Measures for Expanded Urinalysis

- Total protein (quantitative)
- Microalbumin
- β2-microglobulin

1 Plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, IM testing (or possibly for purposes of IM assay development and/or validation), or to assess other actions of volanesorsen with plasma constituents

2 Will be performed on abnormal findings unless otherwise specified

Appendix C Pharmacokinetic Sampling Schedule

Appendix C Pharmacokinetic Sampling Schedule

Blood samples for the determination of plasma volanesorsen concentrations will be collected prior to dosing, and at various times throughout the dosing and post-treatment follow-up period as noted in the tables below.

PK Sampling Schedule (All Patients except PK Subgroup)

Week	Wk 1	Wk 4	Wk 8	Wk 13	Wk 26	Wk 38	Wk 52	Wk 65
Study Day	**D1**	**D22**	**D50**	**D85**	**D176**	**D260**	**D358**	**D449**
Visit Window +/- Days	0	2	2	2	2	3	2	7
Time Point	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime

PK Sampling Schedule (PK Subgroup only*)

Week	Wk 1	Wk 1	Wk 4	Wk 8	Wk 13	Wk 26	Wk 38	Wk 52	Wk 65
Study Day	**D1**	**D2**	**D22**	**D50**	**D85**	**D176**	**D260**	**D358**	**D449**
Visit Window +/- Days	0	0	2	2	2	2	3	2	7
Time Point	Pre-dose, 1, 2, 3, 4, 6, 8, and 12 hrs post-dose	24 hrs post-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime

* Patients at selected sites will be asked to participate in the extended 24-hour PK profile beginning on Study Day 1. Participation is optional

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

The following grading recommendations for adverse events relating to lab test abnormalities are based upon the **Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010**

Adverse Event	Mild	Moderate	Severe
Hematology			
aPTT prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage
Eosinophils increased†	650 – 1,500 cell/mm^3	1,501 - 5,000 cell/mm^3	>5,000 cell/mm^3
Fibrinogen decreased	<1.0 - 0.75 x LLN or <25% decrease from baseline	<0.75 - 0.5 x LLN or 25 - <50% decrease from baseline	<0.5 x LLN or ≥50% decrease from baseline
Hemoglobin decreased (Anemia)	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated
Hemoglobin increased	Increase in >0 - 2 g/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 g/dL above ULN or above baseline if baseline is above ULN	Increase in >4 g/dL above ULN or above baseline if baseline is above ULN
INR increased	>1 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation
Lymphocyte count decreased	<LLN - 800/mm^3; <LLN - 0.8 x 10^9/L	<800 - 500/mm^3; <0.8 - 0.5 x 10^9 /L	<500 /mm^3; <0.5 x 10^9 /L
Lymphocyte count increased	-	>4000/mm^3 - 20,000/mm^3	>20,000/mm^3
Neutrophil count decreased	<LLN - 1500/mm^3; <LLN - 1.5 x 10^9 /L	<1500 - 1000/mm^3; <1.5 - 1.0 x 10^9 /L	<1000/mm^3; <1.0 x 10^9 /L
Platelet count decreased	<LLN - 75,000/mm^3; <LLN - 75.0 x 10^9 /L	<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9 /L	<50,000/mm^3; <50.0 x 10^9 /L
White blood cell decreased	<LLN - 3000/mm^3; <LLN - 3.0 x 10^9 /L	<3000 - 2000/mm^3; <3.0 - 2.0 x 10^9 /L	<2000/mm^3; <2.0 x 10^9 /L
Chemistry			
Acidosis	pH <normal, but >=7.3	-	pH <7.3
Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Alkalosis	pH >normal, but ≤7.5	-	pH >7.5
Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 x ULN
Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

Adverse Event	Mild	Moderate	Severe
Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer
CD4 lymphocytes decreased	<LLN - 500/mm^3; <LLN - 0.5 x 10^9 /L	<500 - 200/mm^3; <0.5 - 0.2 x 10^9 /L	<200/mm^3; <0.2 x 10^9 /L
CPK increased*	>ULN - <6 ULN	6 - 10 x ULN	>10 x ULN
Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 x ULN
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 mg/dL; >3.1 mmol/L; Ionized calcium >1.6 mmol/L; hospitalization indicated
Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 mg/dL; >13.9 mmol/L; hospitalization indicated
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0; hospitalization indicated
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 mg/dL; >1.23 mmol/L
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 mmol/L; hospitalization indicated
Hyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 mg/dL; <1.75 mmol/L; Ionized calcium <0.9 mmol/L; hospitalization indicated
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 mg/dL; <3.0 mmol/L	<40 mg/dL (<2.2 mmol/L) AND requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions‡
Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 mmol/L; hospitalization indicated
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 mg/dL; <0.4 mmol/L
Hyponatremia	<LLN - 130 mmol/L	-	<130 mmol/L
Hypophosphatemia	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 mg/dL; <0.6 mmol/L
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

Adverse Event	Mild	Moderate	Severe
Urine			
Proteinuria Adults Children	1+ proteinuria; urinary protein <1.0 g/24 hrs -	2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs; Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Urinary protein ≥3.5 g/24 hrs; Urine P/C >1.9
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated

†Grading for this parameter is derived from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007

*Grading for this parameter is derived from the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0, Nov 2014

‡Modified for consistency with the ADA and Endocrine Society Guidelines (Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. Diabetes Care 2013;36:1384-95)

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ISIS 304801-CS7

The APPROACH Open Label Extension Study

Volanesorsen (ISIS 304801)

An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol Amendment 3 –9 May 2016

EudraCT No: 2015-003755-21

ISIS 304801-CS7

The APPROACH Open Label Extension Study

Volanesorsen (ISIS 304801)

An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol Amendment 3 – 9 May 2016

Protocol History:

Original Protocol:	28 August 2015
Protocol Amendment 1:	2 February 2016
Protocol Amendment 2:	22 April 2016

Sponsor:

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[redacted] M.D., M.B.A.
[redacted]

Ionis Protocol Number: ISIS 304801-CS7

Protocol Amendment 3

EudraCT No: 2015-003755-21

Clinical Phase: 3

The APPROACH Open Label Extension Study

Volanesorsen (ISIS 304801)

An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

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Date: 9 May 2016

Confidentiality Statement

This document contains confidential information of Ionis Pharmaceuticals, Inc., that must not be disclosed to anyone other than the recipient study staff and members of the independent ethics committee, institutional review board, or authorized regulatory agencies. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc.

Protocol Signature Page

Protocol Number: ISIS 304801-CS7

Protocol Title: An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Amendment: Amendment 3

Date: 9 May 2016

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)", dated 9 May 2016, and agree to conduct the study as described herein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice (E6).

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc.

Investigator's Signature

Investigator's Name *(please print)*

Date (DD Month YYYY)

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PROTOCOL AMENDMENT

Protocol Number:	ISIS 304801-CS7
Protocol Title:	An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Amendment Number:	3
Amendment Date:	9 May 2016

The purpose of this protocol amendment is to implement the following modifications to Protocol ISIS 304801-CS7 Amendment 2 dated 22 April 2016:

1. To add language that any case of a platelet count ≤ 50,000/mm^3 should be reported in an expedited fashion to the Sponsor.
2. To add language regarding the frequency of obtaining platelet counts after a Study Drug dose pause and subsequent rechallenge.
3. To add language that any unreportable platelet count result must be rechecked and determined not to have met a stopping rule before dosing can continue.

Minor administrative changes or corrections (not included in the list of changes) have been made throughout the protocol in order to improve the overall clarity of the protocol but these changes do not impact the study design.

The following table provides a summary list of changes to the protocol:

Protocol Section	Description of Change	Rationale
Section 6.2.1 Laboratory Assessments Section 8.5.2 Safety Monitoring for Platelet Count Results Appendix A Schedule of Procedures	Any case of a platelet count ≤ 50,000/mm^3 should be reported in an expedited fashion to the Sponsor	To ensure that Sponsor is aware in a timely fashion of platelet counts performed in local lab that have met the rule for dose pause
Section 8.6.3 Stopping Rules for Platelet Count Results	Following a rechallenge platelet count should be tested every week until count is stable	To more closely monitor platelet levels following a rechallenge
Section 6.2.1 Laboratory Assessments Section 8.6.3 Stopping Rules for Platelet Count Results Appendix A Schedule of Procedures	Any unreportable platelet count result must be rechecked and determined not to have met a stopping rule before dosing can continue	To provide added patient safety regarding platelet stopping rules

PROTOCOL SYNOPSIS

Protocol Title	An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Study Phase	3
Indication	Familial Chylomicronemia Syndrome
Study Objectives	To evaluate the safety and efficacy of extended dosing with volanesorsen (volanesorsen sodium 300 mg) in patients with FCS
Study Design	This is a multi-center, open-label extension study of ISIS 304801-CS6 and ISIS 304801-CS16. All patients will receive volanesorsen 300 mg once per week for 52 weeks. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period. Following the Week 52 visit, patients will enter a 13-week post-treatment evaluation period.
Number of Patients	Up to approximately 70 patients dosed
Study Population	Inclusion Criteria: 1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law 2. Age ≥ 18 years at time of informed consent 3. Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement. Patients who are enrolled in ISIS 304801-CS16 must also meet the following criteria in order to enter into the Extension Study: a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L) b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) by documentation of at least 1 of the following: • Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1) • Post heparin plasma LPL activity of ≤ 20% of normal c. Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 study 4. Able and willing to participate in a 65-week study 5. Satisfy 1 of the following: a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved), abstinent*, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration

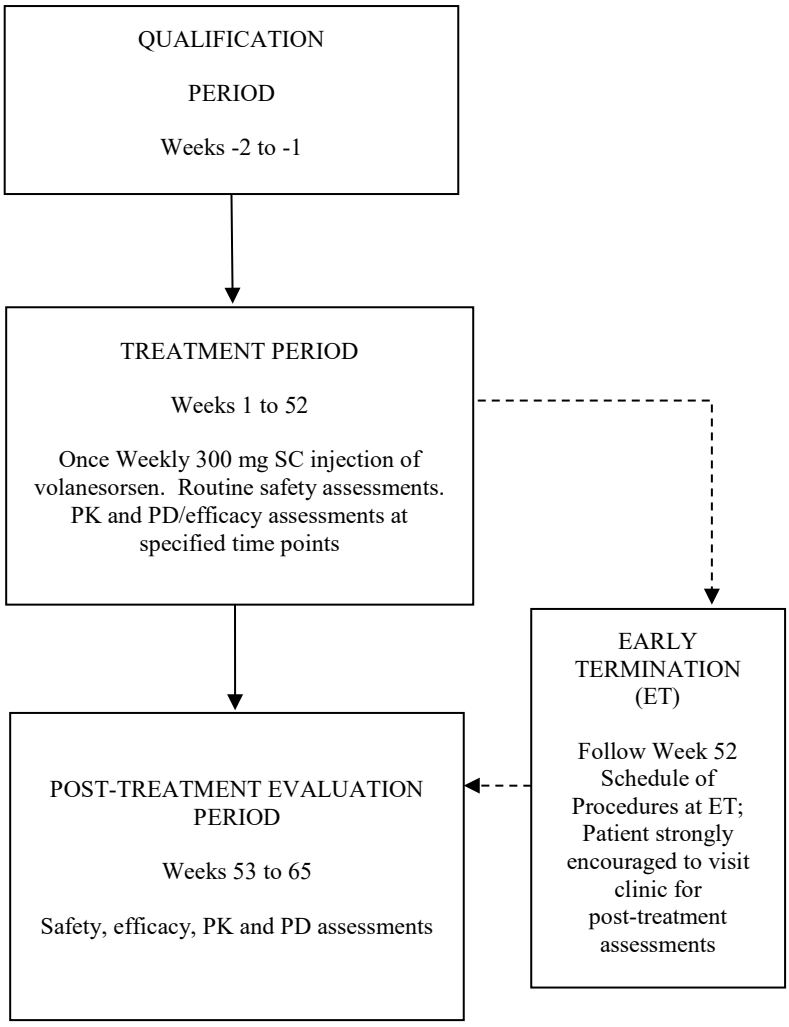
PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	Inclusion Criteria: *Continued* b. Males: Surgically sterile, abstinent* or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration * Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception Exclusion Criteria: 1. Have any new condition or worsening of existing condition which in the opinion of the Investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study 2. Unwilling to comply with lifestyle requirements for the duration of the study (Section 6.3)
Treatment Group	Volanesorsen 300 mg once per week
Study Drug Administration	Volanesorsen will be administered as subcutaneous (SC) injections.
Dose Adjustments	Dose adjustments, including dose interruptions and/or decreasing the dose frequency will be allowed for safety or tolerability after consultation with the Sponsor Medical Monitor.
Rationale for Dose and Schedule Selection	The dose of 300 mg once weekly was chosen for the double-blinded placebo-controlled Phase 3 index studies (ISIS 304801-CS6- and ISIS 304801-CS16) based on the pharmacodynamic and safety analysis of the Phase 2 studies which included a subset of patients with FCS. This is an extension to the ISIS 304801-CS6 and ISIS 304801-CS16 index studies. Only the subset of patients from ISIS 304801-CS16 with FCS diagnosis may enter the Extension Study. (Please refer to inclusion criteria #3, above)
Study Visit Schedule and Procedures	The study for an individual patient will generally consist of the following periods: • A qualification period of up to 2 weeks (unless approved by the Sponsor). Please refer to Section 4.1 and Appendix A. A 52-week treatment period during which volanesorsen will be administered as a once weekly SC injection • A 13-week post-treatment evaluation period The patients, Investigators, study staff, and the Sponsor will remain blinded to lipid data through the last patient's Week 13 visit of the extension study or until results from the database locks for the ISIS 304801-CS6 and ISIS 304801-CS16 index studies becomes available, whichever comes first. Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), adverse events (AE), concomitant medication/procedure information, lipid panel, volanesorsen plasma concentrations, immunogenicity (IM) testing, liver/spleen magnetic resonance imaging (MRI), ECGs, echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Dietary counseling will be repeated at intervals throughout the treatment and follow-up period and a daily food/drink diary will be completed for the week prior to each quarterly visit by each patient. Following the Week 52 visit, patients will enter the 13-week post-treatment evaluation period.

PROTOCOL SYNOPSIS *Continued*

Safety and Tolerability Evaluations	Overall safety and tolerability of volanesorsen will be assessed by determining the incidence and severity of adverse and serious adverse events (including independently adjudicated events of acute pancreatitis and MACE), withdrawals due to adverse events, and changes in laboratory and other safety parameters.
Planned Analyses	Safety Endpoints: • Adverse events including adjudicated events of acute pancreatitis and MACE • Vital signs and weight • Physical examinations • Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis) • Echocardiography • Electrocardiograms (ECGs) • Use of concomitant medications • MRIs Efficacy Endpoints: • Percent change and absolute change from baseline in fasting TG • Frequency and severity of patient reported abdominal pain during the treatment period • Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-high-density lipoprotein-cholesterol (non-HDL-C), apolipoprotein B [apoB], high-density lipoprotein-cholesterol (HDL-C), apolipoprotein A-1 [apoA-1], very-low-density lipoprotein-cholesterol (VLDL-C), and LDL-C • Percent change from baseline in fasting total apolipoprotein C-III (apoC-III) • Quality of Life questionnaires (EQ-5D, SF-36) • Adjudicated acute pancreatitis event rate • Other symptoms: eruptive xanthoma, lipemia retinalis
Pharmacokinetic Evaluations	Plasma samples will be taken from all patients for the measurement of volanesorsen as follows: trough levels (pre-dose) throughout treatment and post-treatment levels during the post-treatment follow-up period. In a subset of patients, more frequent assessment of plasma concentrations of volanesorsen will be performed to determine volanesorsen pharmacokinetic parameters. Plasma sample collection time points are detailed in Appendix A and Appendix C.
Statistical Considerations	No sample size calculations were performed as this is an extension study to the double-blind placebo controlled ISIS 304801-CS6 and ISIS 304801-CS16 index studies.
Sponsor	Ionis Pharmaceuticals, Inc.
Collaborator	Akcea Therapeutics

STUDY DESIGN AND TREATMENT SCHEMA



STUDY GLOSSARY

Abbreviation/Acronym	Definition
ADA	anti-drug antibody
AE	adverse Event
ALP	alkaline Phosphatase
ALT	alanine Aminotransferase
ANA	antinuclear Antibody
apoA-1	apolipoprotein A-1
apoB	apolipoprotein B
apoC-III	apolipoprotein C-III
apoE	apolipoprotein E
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
CBC	complete blood count
C_{max}	maximum observed drug concentration
CRF	case report form
DNA	deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
ET	early termination
FAS	full analysis set
FCS	Familial Chylomicronemia Syndrome
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
GPIHBP1	Glycosylphosphatidylinositol-anchored HDL-binding Protein 1
HAPI	Heritability and Phenotype Intervention
HbA1c	Glycated Hemoglobin
HDL	High-Density Lipoprotein
HDL-C	High-Density Lipoprotein-Cholesterol
hsCRP	High-sensitivity C-reactive protein
ICH	International Conference on Harmonization
IDL	Intermediate density lipoprotein
IEC	Independent Ethics Committee
IM	immunogenicity
Index Studies	ISIS 304801-CS6 and ISIS 304801-CS16

INR	International Normalized Ratio
IRB	Institutional Review Board
IXRS	Interactive Voice/Web-Response System
LDL	Low-Density Lipoprotein
LDL-C	Low-Density Lipoprotein-Cholesterol
LMF1	Lipase Maturation Factor 1
LPL	Lipoprotein Lipase
MACE	Major Acute Cardiovascular Event
MOE	2′-*O*-(2-methoxyethyl)
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NCS	not clinically-significant
NOAEL	No-Observed-Adverse-Effect Level
non-HDL-C	Non-High-Density Lipoprotein-Cholesterol
OLE	Open Label Extension
OTC	over the counter
PFS	prefilled syringe
PD	pharmacodynamic
PK	pharmacokinetic
PPS	per protocol set
PT	prothrombin time
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SUSAR	suspected unexpected serious adverse reaction
T2DM	type 2 diabetes mellitus
T_{max}	time to maximal concentration
TG	triglycerides
Treatment-emergent	occurring after first dose of Study Drug
TRL	Triglyceride-Rich Lipoproteins
ULN	upper limit of normal
VLDL	Very-Low-Density Lipoprotein
VLDL-C	Very-Low-Density Lipoprotein-Cholesterol
VLDL-TG	Lipoprotein-Triglyceride
WMA	World Medical Association

1. OBJECTIVES

The objective of the study is to evaluate the safety and efficacy of extended dosing with volanesorsen in patients with familial chylomicronemia syndrome.

2. BACKGROUND AND RATIONALE

2.1 Overview of Disease

Familial Chylomicronemia Syndrome (FCS) is an inherited disease characterized by severe hypertriglyceridemia and chylomicronemia, and risk or history of pancreatitis. It is a rare autosomal recessive disease that can be diagnosed either in childhood or adulthood.

Fasting plasma triglyceride (TG) levels in FCS patients are typically 10-fold to 100-fold above normal (1,500 to 15,000 mg/dL), despite extreme dietary fat restriction (20 g or approximately 15-20% of daily calorie intake) (Brunzell 1999-2011). Patients with FCS often present in infancy or childhood with frequent and severe abdominal pain, repetitive colicky pain, repeated episodes of potentially fatal acute pancreatitis, and failure to thrive (Brunzell 1999-2011; Tremblay et al. 2011). Physical examination frequently reveals eruptive xanthomas, lipemia retinalis and hepatosplenomegaly, and plasma from patients appears lactescent, interfering with determination of other laboratory parameters (Tremblay et al. 2011).

Patients with fasting triglyceride levels > 10 mmol/L probably have a component of chylomicronemia. Clinical diagnosis would include evidence of clinical features of chylomicronemia syndrome and secondary causes such as uncontrolled type 1 or type 2 diabetes mellitus (T2DM), hypothyroidism, poor diet, alcohol use, nephrotic syndrome or use of associated medications should be ruled out. The diagnosis of FCS may be made more specifically by genotyping or confirmation of very low or absent lipoprotein lipase (LPL) enzyme activity in post heparin plasma (Brunzell 1999-2011).

Patients with FCS carry a heavy burden of medical complications, the most serious, as described above, being an extreme risk of recurrent and potentially fatal pancreatitis. Due to the recurrent episodes of acute pancreatitis, these patients may also develop chronic pancreatitis and signs of exocrine or endocrine pancreatic insufficiency, including diabetes mellitus (Gaudet et al. 2013). While the pathophysiology underlying chylomicron-related pancreatitis has not been completely elucidated, 1 hypothesis is that large chylomicrons lodged in pancreatic capillaries are exposed to pancreatic lipase, with the subsequent release of free fatty acids through the hydrolysis of chylomicron-associated TGs. High concentrations of free fatty acids are thought to damage pancreatic cells leading to emergent pancreatitis (Yang et al. 2009; Berglund et al. 2012).

The etiology of extreme hypertriglyceridemia in FCS is considered to be ineffective triglyceride clearance, due to an extremely low level of LPL activity. LPL normally functions to hydrolyze triglycerides (TG) in chylomicrons along the luminal surface of capillaries, mainly in heart, skeletal muscle, and adipose tissue, promoting triglyceride clearance from the circulation. LPL is regulated by a number of key genes, and loss-of-function mutations in one of these genes, or the LPL gene itself, results in FCS (Surendran et al. 2012). In addition to loss of function mutations, null mutations, and nonsense mutations in the LPL gene, other genes currently identified in FCS patients, and known to directly influence LPL activity include: apolipoprotein C-II (APOC2) a cofactor for LPL (Schuster et al. 2011); apolipoprotein A-V

(APOA5) an enhancer of LPL activity (Schaap et al. 2004); lipase maturation Factor 1 (LMF1), a transmembrane protein involved in LPL maturation (Doolittle et al. 2009); glycosylphosphatidylinositol-anchored HDL-binding protein 1 (GPIHBP1), a capillary endothelial cell protein that provides a platform for LPL-mediated processing of chylomicrons (Beigneux et al. 2007).

2.2 Therapeutic Rationale

Apolipoprotein C-III (ApoC-III), a key regulator of plasma triglyceride levels, is a 79 amino acid glycoprotein synthesized principally in the liver (Ooi et al. 2008; Figure 1). ApoC-III is a major regulator of lipoprotein metabolism and plays a pivotal role in regulating plasma TG levels (Chan et al. 2008). It is a component of triglyceride-rich lipoproteins (TRLs) and a potent inhibitor of LPL (Lemieux et al. 2003). At higher concentrations apoC-III also inhibits hepatic lipase activity (Kinnunen and Ehnolm 1976), an enzyme which plays an important role in the conversion of dense very-low-density lipoprotein (VLDL) to intermediate density lipoprotein (IDL) and to LDL (Mendivil et al. 2010), as well as in the remodeling of HDL (Brown et al. 2010). In addition, increased apoC-III content adversely affects apoE-mediated hepatic uptake of TG-rich remnants (Mann et al. 1997). Thus, elevated plasma apoC-III levels are associated with impaired hydrolysis and retarded clearance of TG-rich particles, resulting in the accumulation of lipoprotein-triglyceride (VLDL-TG) and chylomicrons in plasma and the development of hypertriglyceridemia (Ito et al. 1990).

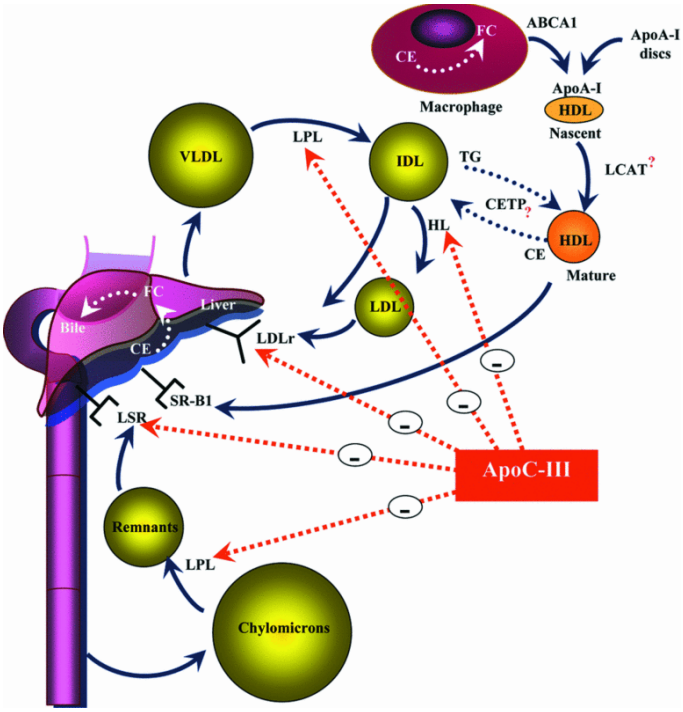


Figure 1 ApoC-III Regulates Lipoprotein Metabolism by Multiple Mechanisms

From Ooi et al. 2008; ABCA1 = ATP-binding cassette A1, apo = apolipoprotein, CE = cholesterol ester, CETP = cholesterol ester transfer protein, FC = free cholesterol, HDL = high-density lipoprotein, HL = hepatic lipase, IDL = intermediate-density lipoprotein, LCAT = lecithin cholesterol acyltransferase, LDL = low-density lipoprotein, LDLr = LDL receptor, LPL = lipoprotein lipase, LSR = lipolysis-stimulated receptor, SR-B1 = scavenger receptor B-1, TG = triglyceride, VLDL = very low-density lipoprotein.

Mechanistically, FCS is primarily a consequence of ineffective clearance of TRL. ApoC-III is a prominent component of TRL (e.g., VLDL and chylomicrons). In addition to its role in inhibiting LPL, apoC-III inhibits TRL remnant (TG-depleted remnant lipoprotein) uptake by hepatic lipoprotein receptors by steric inhibition of the interaction of apoE with these receptors.

Human genetic data have demonstrated positive phenotypic associations with loss (e.g., null or nonsense mutations) and negative effects with gain of function mutations (Atzmon et al. 2006; Pollin et al. 2008; Petersen et al. 2010). A novel nonsense mutation in the apoC-III gene was identified in the heritability and phenotype intervention (HAPI) heart study in Old Order Amish that results in lower plasma apoC-III and TG levels and lower LDL-C, increased HDL-C and reduced atherosclerosis (Pollin et al. 2008). In another study involving a group of 214 Ashkenazi Jews of advanced age (had passed or nearly reached 100 years of age), genotype analysis revealed a polymorphism in the apoC-III gene (APOC3-641CC genotype) with a clear pattern of age-dependent frequency that was associated with significantly lower levels of apoC-III protein, a favorable lipoprotein profile and increased longevity (Atzmon et al. 2006). In contrast to the Amish and Ashkenazi apoC-III polymorphisms associated with lower plasma TG, apoC-III polymorphisms associated with higher plasma TG have also been recently described (Petersen et al. 2010). In a cohort of lean (mean body mass index [BMI] = 24.7 ± 3.6 kg/m^2) Asian Indians, carriers of apoC-III variant alleles (C-482T, T-455C, or both) were noted to have significantly higher plasma apoC-III and TG levels, and decreased ability to clear postprandial plasma TG from the circulation. Taken together, the available data strongly support the development of a therapy that reduces plasma apoC-III levels in order to reduce the very high circulating triglyceride and chylomicron levels that are accompanied by increasing risk for acute pancreatitis.

Given the profound reductions in TGs observed with volanesorsen treatment in FCS patients who have no detectable LPL activity (See Section 2.3.4), and the mechanistic data available to date on apoC-III function, potential mechanisms that explain how apoC-III inhibition results in triglyceride reduction in FCS patients include: (1) enhancing the very small residual amounts of LPL activity that these patients may have, below the limit of detection of the assay in many cases (2) potentially enhanced activity of other lipases also involved in the metabolism and breakdown of TGs, such as hepatic lipase or endothelial lipase (Kinnunen and Ehnolm 1976), and (3) apoC-III interaction with Apolipoprotein E (apoE), an important factor in liver reuptake of lipid particles by blocking apoE-mediated uptake of lipid particles in the liver (Breyer et al. 1999), and therefore, reducing apoC-III might enhance apoE-mediated uptake of lipid particles. Volanesorsen-mediated reduction of apoC-III could be contributing to one or all of these mechanisms resulting in the observed potent and sustained reductions in TG.

Through a novel apoC-III lowering mechanism of action, volanesorsen may provide the potential to manage triglyceride levels in FCS patients.

2.3 Volanesorsen

2.3.1 Mechanism of Action

Volanesorsen is a second-generation antisense oligonucleotide (ASO) drug targeted to human apoC-III. It is complementary to a region within the 3′ untranslated region of the apoC-III messenger ribonucleic acid (mRNA) and binds to the mRNA by Watson and Crick base pairing.

The hybridization (binding) of volanesorsen to the cognate mRNA, results in the RNase H1-mediated degradation of the apoC-III mRNA, thus preventing production of the apoC-III protein. Maximal antisense-mediated reduction of target mRNA levels is typically greater than 90% of control levels in sensitive tissues (Crooke and Bennett 1996; Zhang et al. 2010). Furthermore, reduction in target mRNA levels using this approach correlates directly with a subsequent reduction in target protein levels.

2.3.2 Chemistry

Chemically, volanesorsen is a synthetic oligomer of 20 nucleotides (i.e., a 20-mer) that are connected sequentially by phosphorothioate linkages. The nucleotide sequence of volanesorsen (Figure 2) is complementary to a 20-nucleotide stretch within the 3′ untranslated region of the apoC-III mRNA transcript at base position 489-508. Structurally, the oligonucleotide has 3 regions. Two (2) of them, the 5 nucleotides at the 5′ end and the 5 nucleotides at the 3′ end, are composed of 2′-*O*-(2-methoxyethyl) (MOE)-modified ribonucleotides. These MOE-modified nucleotides confer (1) increased affinity to the target mRNA (Altmann et al. 1996; McKay et al. 1999), (2) increased resistance to exonucleases and endonucleases (thereby increasing stability in tissue) (Geary et al. 2003), and (3) amelioration of some of the high dose toxicities thereby resulting in an improved safety profile compared to first generation antisense drugs containing phosphorothioate modified oligodeoxynucleotides (DNA) (Henry et al. 2000). The third region, the central portion of the oligonucleotide, is composed of 10 oligodeoxynucleotides. This chimeric design is called a MOE-Gapmer, and volanesorsen employs this chimeric structure to enable use of the RNase H1-mechanism for antisense activity. This is because while the 2′-MOE modification confers increased stability and affinity, it does not support RNase H1 catalysis of RNA hybridized to 2′-MOE-modified nucleotides (McKay et al. 1999). This is caused by conformational changes induced in the heteroduplex by 2′-alkoxy:RNA hybrids that are not recognized by RNase H1 enzymes (Inoue et al. 1987; Monia et al. 1993). By limiting the 2′-MOE modification to nucleotides flanking the phosphorothioate oligodeoxynucleotide core, the beneficial attributes of the 2′-MOE chemistry are preserved while also retaining RNase H1 recognition.

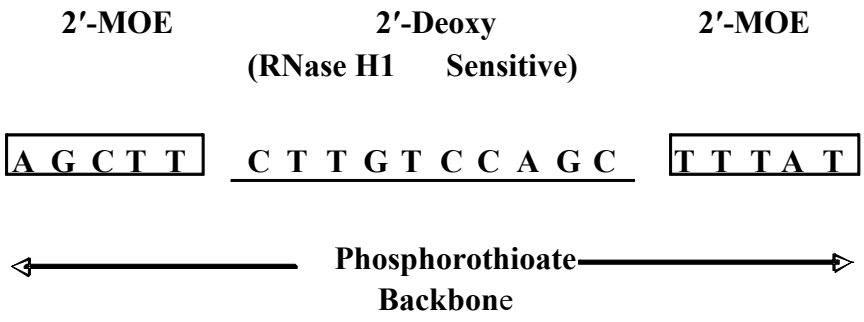


Figure 2 Design of Chimeric 2′-MOE Phosphorothioate Oligonucleotides (MOE-Gapmer). The sequence of volanesorsen is shown

2.3.3 Preclinical Experience

Inhibition of apoC-III using volanesorsen has been shown to potently reduce hepatic apoC-III mRNA as well as plasma apoC-III protein and TG in a dose- and time-dependent fashion in several species, including human apoC-III transgenic mice, and other rodent and monkey models. Treatment with volanesorsen also resulted in reduced VLDL and chylomicron TG and reduced postprandial TG in hypertriglyceridemic monkeys (Graham et al. 2013).

The pharmacokinetics (PK) and toxicity of volanesorsen have been assessed in mice, rats, and cynomolgus monkeys. General toxicity studies with volanesorsen for up to 39 weeks of treatment followed by up to a 20-week recovery period are complete. The preclinical toxicology program for volanesorsen consists of single dose safety pharmacology studies in the monkey (cardiovascular) and mouse (neurobehavioral and pulmonary assessment studies), *in vitro* and *in vivo* genetic toxicity assessment, repeat dose fertility and/or developmental reproductive toxicology studies in the mouse and rabbit and evaluation in the *in vitro* human Ether-á-go-go-related gene (hERG) assay.

Volanesorsen treatment-related findings in mice and monkeys were generally consistent with those expected for the 2′-MOE-class of ASOs. Treatment-related findings included effects consistent with drug accumulation in tissues in rodents and monkeys, species-dependent proinflammatory response in rodents and monkeys and complement activation and reductions in platelet counts in the monkey. In the mouse and monkey general toxicity studies, reduction of hepatic apoC-III mRNA (> 75%) was not associated with any findings that could be considered related to the pharmacologic inhibition of apoC-III for up to 39 weeks of treatment.

The long-term, chronic toxicology studies in rodents with volanesorsen produced a significant proinflammatory response that led to subsequent effects on the heart at high doses. The rodent species are most sensitive to the proinflammatory effects of antisense molecules. Importantly, these effects on the heart were not observed in the monkey chronic toxicity studies even at the highest doses tested where drug exposure was higher than that in rodents.

Because these changes were not observed in monkeys, the findings in the heart are considered to be rodent-specific and not relevant to humans. Nevertheless, such effects will be monitored by measurement of echocardiograms that will be included in this clinical study.

Volanesorsen caused no untoward effects in safety pharmacology studies (*in vitro* and *in vivo*) and was non-genotoxic (*in vitro* and *in vivo*). Volanesorsen had no effects on fertility or embryo/fetal development in the mouse or rabbit reproductive toxicity studies. In these studies, volanesorsen was detected in placental tissue but not in fetal tissue indicating that little, if any, drug was able to cross the placenta to reach the fetus. Reduction of apoC-III mRNA (64% in males and 47% in females) also did not affect fertility or cause untoward effects on embryo/fetal development in mice.

Detailed information concerning the preclinical studies conducted with volanesorsen can be found in the volanesorsen Investigator's Brochure.

2.3.4 Clinical Experience

Detailed information concerning the clinical studies conducted with volanesorsen can be found in the volanesorsen Investigator's Brochure. A summary is included below.

Volanesorsen has been evaluated in one Phase 1 study and two Phase 2 studies, all double blinded and placebo controlled. The total exposures comprise 99 patients and healthy volunteers administered volanesorsen from 50 to 400 mg subcutaneously up to 3 months (compared to 37 administered placebo).

All clinical trials of volanesorsen have shown large and clinically meaningful reductions in fasting plasma apoC-III and TG (~80% and 70%, respectively, mean reduction from baseline with 300 mg dose) with a very high degree of consistency of response between the different patient groups. This includes healthy volunteers, patients with moderate to severe hypertriglyceridemia not on background TG-lowering therapy, patients with moderate to severe hypertriglyceridemia on a background stable fibrate therapy (Gaudet et al. 2015), patients with FCS, and patients with T2DM.

In a Phase 2 study, 3 patients with FCS were treated with 300 mg/wk volanesorsen in an open label fashion. These patients had a mean baseline fasting TG level of 1,844 mg/dL and all 3 patients achieved TG levels below or close to 500 mg/dL during the dosing period out to Day 92 (Figure 3). Two (2) of the FCS patients had an absolute reduction in fasting TG in excess of 1,500 mg/dL (Gaudet et al. 2014).

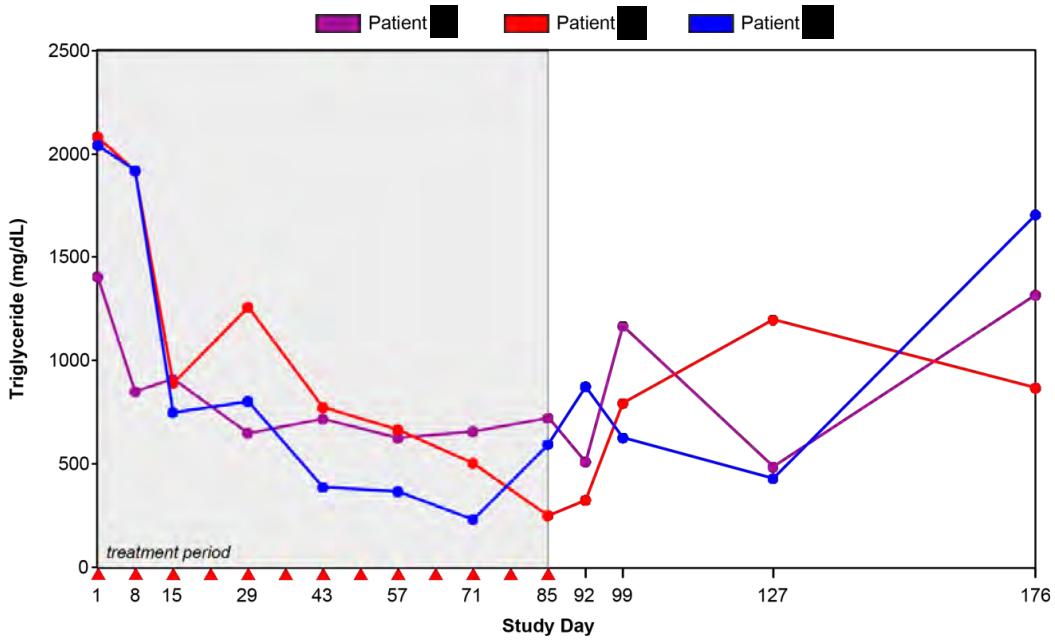


Figure 3 Fasting Triglycerides in Patients with FCS Treated with Volanesorsen

In clinical studies conducted to date volanesorsen has been well-tolerated and has shown a favorable safety profile. There has been no clinical or laboratory evidence of drug-drug interactions.

In the completed studies there have been no volanesorsen associated laboratory abnormalities suggestive of an effect on the renal (serum creatinine, proteinuria) or hepatic systems (alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin). In Phase 2 studies, there was a mild decrease of platelet count associated with volanesorsen administration that recovered in the post-treatment period and was not associated with platelet-related adverse events (AEs). In the blinded ongoing clinical trials of ISIS 304801, 2 patients of 142 dosed (as of February 29, 2016) had a decrease in platelet count to less than 50,000/mm^3 in the absence of major bleeding or clinically-relevant non-major bleeding and had Study Drug paused as per the monitoring and stopping rules for platelet counts (Section 8.6.3). Platelet counts recovered following suspension of dosing.

The most frequently observed AEs with volanesorsen were local reactions at the injection site. Local cutaneous reactions at the injection site defined as those events presenting as either pain, tenderness, erythema, pruritus or swelling occurring on the day of injection and persisting for at least 2 days were infrequent (~15% of injections), were almost always mild, resolved spontaneously, were non-progressive, and were not associated with systemic sequelae.

2.4 Rationale for Dose and Schedule of Administration

The dose and schedule selected for this study is 300 mg per week for 52 weeks. The dose of 300 mg per week is supported by both the cumulative nonclinical data available to date and the Phase 2 clinical data. In nonclinical studies, volanesorsen treatment-related effects in rodents and monkeys were consistent with drug accumulation in tissues and also include species-specific proinflammatory responses. In the monkey, the No-Observed-Adverse-Effect Level (NOAEL) was defined by the cumulative clinical pathology results and histopathology data which provide an adequate clinical margin. No nonclinical findings were considered to be related to the pharmacologic inhibition of apoC-III.

The safety data to date suggest that volanesorsen has been well-tolerated at dose levels up to 300 mg in patients with high triglycerides (including type 2 diabetes patients and administration in combination with fibrates and statins) with the most common AEs being local to the injection site and predominantly mild. A pooled analysis of safety for the Phase 2 studies did not demonstrate any clear difference in safety or tolerability between the different doses tested (100 mg, 200 mg, and 300 mg per week for 13 weeks).

Analysis of the cohorts in which volanesorsen was studied at different doses demonstrates dose-dependent pharmacology with respect to pharmacodynamic (PD) effect on the target, apoC-III, with a clear difference in the TG-lowering effect between the different doses in the 100 mg to 300 mg dose range as compared to placebo.

In addition to the nonclinical and clinical experience of volanesorsen, the dose and schedule of administration is supported by the preclinical and clinical safety experience of several other 2′-MOE-modified ASOs that have been safely administered intravenously and subcutaneously in multiple clinical studies at doses up to 1000 mg and for treatment durations that exceed 24 months (Santos et al. 2015).

3. EXPERIMENTAL PLAN

3.1 Study Design

This is an open-label extension to the Phase 3 study of volanesorsen in patients with FCS (ISIS 304801-CS6 or ISIS 304801-CS16). Up to approximately 70 patients will receive 300 mg once weekly volanesorsen for 52 weeks.

Following the Week 52 visit, patients enter a 13-week post-treatment evaluation period.

3.2 Number of Study Centers

This study will be conducted at multiple centers worldwide.

3.3 Number of Patients

Up to approximately 70 patients will be dosed.

3.4 Overall Study Duration and Follow-up

The Study will consist of the following periods:

- A qualification period of up to 2 weeks (unless approved by the Sponsor). Please refer to Section 4.1 and Appendix A.
- A 52-week treatment period during which volanesorsen will be administered as a once weekly SC injection
- A 13-week post-treatment evaluation period

Please refer to the Schedule of Procedures in Appendix A.

3.4.1 Qualification

A period of up to 2 weeks is given to complete qualification assessments outlined in the Schedule of Procedures (Appendix A).

3.4.2 Treatment

The treatment period is 52 weeks. Eligible patients will report to the Study Center for assessments at specified intervals throughout the 52-week treatment period as detailed in the Schedule or Procedures (Appendix A). During the treatment period, volanesorsen is administered by SC injection once weekly.

3.4.3 Post-Treatment

The post-treatment evaluation period is 13 weeks and consists of 2 Study Center visits on Weeks 58 and 65.

3.5 End of Study

The End-of-Study is last patient, last visit.

3.6 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will review (as needed) safety, tolerability and efficacy data collected on volanesorsen during this study. Based on its ongoing assessment of the safety and tolerability of volanesorsen, the DSMB will provide recommendations to the Sponsor for modifying, stopping or continuing the study as planned. Details on the safety assessments, frequency of review and meeting schedules are outlined in the DSMB Charter and/or the statistical analysis plan (SAP).

4. PATIENT ENROLLMENT

4.1 Qualification

Before patients may be enrolled into the study, the Sponsor requires a copy of the Study Center's written independent ethics committee/institutional review board (IEC/IRB) approval of the protocol, informed consent form, and all other patient information.

Patients or their legally acceptable representatives must sign the consent form before any study-specific procedures or evaluations related to this open label study are performed. During the qualification period, the eligibility of the patient to continue in the extension study will be determined. Final assessments from the ISIS 304801-CS6 or ISIS 304801-CS16 studies may be used for qualification. A period of up to 2 weeks after completion of the ISIS 304801-CS6 or ISIS 304801-CS16 index studies (unless approved by the Sponsor) is given to complete qualification. Qualified patients will retain the unique patient identification number that was assigned to them during the ISIS 304801-CS6 or ISIS 304801-CS16 index studies. The patient identification number will be used to identify the patient throughout the extension trial and must be used on all study documentation related to that patient. The patient identification number must remain constant throughout the extension trial.

4.2 Enrollment

Patients will be enrolled after all qualification assessments have been completed and after the Investigator has verified that they are eligible per criteria in Sections 5.1 and 5.2. No patient may begin treatment prior to enrollment.

Eligible patients will be enrolled using an Interactive Voice/Web-Response System (IXRS).

5. PATIENT ELIGIBILITY

To be eligible to participate in this study candidates must meet the following eligibility criteria within 2 weeks of Study Day 1, or at the time point specified in the individual eligibility criterion listed.

5.1 Inclusion Criteria

1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law
2. Age ≥ 18 years at time of informed consent
3. Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement. Patients who are

enrolled in ISIS 304801-CS16 must also meet the following criteria in order to enter into the Extension Study:

a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L)

b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) by documentation of at least 1 of the following:

- Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1)
- Post heparin plasma LPL activity of ≤ 20% of normal

c. Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 study.

4. Able and willing to participate in a 65-week study

5. Satisfy 1 of the following:

a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved), abstinent*, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration.

b. Males: Surgically sterile, abstinent* or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration.

* Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception

5.2 Exclusion Criteria

1. Have any new condition or worsening of existing condition which in the opinion of the Investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study.

2. Unwilling to comply with lifestyle requirements for the duration of the study (Section 6.3).

6. STUDY PROCEDURES

6.1 Study Schedule

All required study procedures are outlined in Appendices A, B, C, and D.

6.1.1 Qualification

Please refer to Section 4.1 and Appendix A.

6.1.2 Treatment Period

The patients, Investigators, study staff, and the Sponsor will remain blinded to lipid data through the last patient's Week 13 visit of the extension study or until results from the database locks for the ISIS 304801-CS6 and ISIS 304801-CS16 index studies become available, whichever comes first.

During the treatment period, patients will report to the study center for clinic visits a minimum of 5 times during Weeks 1-52 (see Schedule of Procedures in Appendix A). Study Drug will be administered once weekly (Section 8.1). Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), AEs, concomitant medication/procedure information, lipid panel, volanesorsen plasma concentrations, immunogenicity (IM) testing, liver/spleen MRI, ECGs, echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Adverse events at the injection site should be collected as adverse events. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period and all patients will complete a daily food diary for one week prior to their quarterly visit. All blood and urine samples should be collected prior to volanesorsen administration. Blood sampling at Weeks 4, 8, 12, 16, 19, 22, 25, 29, 32, 35, 41, 44, 47, 51, and 58 may be conducted by a home healthcare nurse . Approval for study procedures to be conducted by a home healthcare nurse on other outpatient visit days will require prior approval by the Sponsor. Patients must be fasted prior to drawing all blood samples and samples drawn locally must be sent to the central laboratory for analysis. Every effort should be made to ensure the previous week's dose is given 7 days prior to a scheduled clinic visit. Dosing instructions and training will be provided to the patient where applicable.

All reasonable attempts should be made to ensure compliance with the visit schedule as outlined in Appendix A. However, in the event that a visit does not occur or is delayed, all subsequent visits should be calculated based on the time elapsed since Day 1 rather than from the date of the previous visit.

6.1.3 Pharmacokinetic (PK) Subgroup

A subgroup of patients will participate in an extended PK collection. Patients in this subgroup will have more frequent PK sampling over a 24-hour period following the first dose on Study Day 1 in order to evaluate the plasma PK parameters of volanesorsen. Patients in this subgroup will have an additional visit to the clinic, or by a home healthcare nurse, on Day 2 to collect a 24-hour post-dose blood draw after dosing on Day 1. The detailed PK sampling schedules are outlined in Appendix C.

Participation in the PK subgroup is optional for sites and patients, and consent may be withdrawn for the subgroup-specific procedures (e.g., multiple blood draws for PK) without being withdrawn from the study. If a patient withdraws consent from the subgroup procedures, he/she should remain on study and continue to follow all the non-subgroup assessments and procedures as outlined in Appendix A.

6.1.4 Post-Treatment Period

After completion of the Week 52 visit assessments, patients will enter the 13-week post-treatment evaluation period. This period consists of 2 Study Center visits on Weeks 58 and 65 as outlined in the Schedule of Procedures in Appendix A.

6.2 Additional Study Assessments

6.2.1 Laboratory Assessments

Laboratory analyte samples will be collected throughout the study. A list of these analytes is contained in Appendix B.

Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1-week and determined not to have met a stopping rule before dosing can continue.

Any case of a platelet count $\leq 50{,}000/mm^3$ should be reported in an expedited fashion to the Sponsor.

6.2.2 Physical Exams and Vital Signs

Physical exams and vital signs will be performed as indicated in the Schedule of Procedures (Appendix A). Vital signs should include weight, blood pressure, pulse rate, respiratory rate and body temperature. Blood pressure and pulse rate will be recorded after the patient has been in a sitting position for at least 5 minutes. Semi-supine systolic and diastolic blood pressure should always be measured on the same arm (preferentially on the left arm). Height will be measured at the Day 1 visit.

6.2.2.1 Eruptive Xanthoma

At each visit, patients will be asked whether they have had any episodes of eruptive xanthoma since their last visit and the number/duration of the events will be recorded. Physical exams should also include skin examination for presence/resolution of eruptive xanthomas. If a patient experiences an episode of eruptive xanthoma during the study, photos of the area should be taken, if possible.

6.2.2.2 Lipemia Retinalis

If possible, lipemia retinalis will be assessed by fundus photography prior to administration of the first dose of Study Drug (for ISIS 304801-CS16 rollover patients) and repeated at Week 52. Images will be evaluated by an independent assessor, blinded to the patient's treatment assignment.

6.2.3 Echocardiography

Echocardiography for assessment of left and right ventricular function and mitral and aortic valve function will be conducted at Week 26 and Week 52 in all patients. For the purpose of assessment of treatment-emergent changes, all echocardiograms will be evaluated on an ongoing basis by an independent central reader. Results will be provided to the DSMB for their review.

6.2.4 ECG

The ECG will be recorded after the patient has been resting in a supine position for at least 5 minutes. ECGs will be performed in triplicate at Week 13, Week 26, Week 38, Week 52, and Week 65.

6.2.5 MRI

MRI of the liver and spleen will be conducted at Week 52 for all patients for whom MRI is not contraindicated, e.g., patients having metal implants.

MRIs will be conducted using standardized procedures and settings. MRIs will be read by an independent central reader to assess liver fat and liver and spleen size**.**

6.2.6 Quality of Life Assessments

All patients will complete Quality of Life Questionnaires (EQ-5D and SF-36) at Week 1, Week 13, Week 26, Week 52, and Week 65.

6.2.7 Disease Symptom Diary

All patients will complete a symptom questionnaire once a week starting at the beginning of the qualification period and continuing to the end of the post-treatment follow-up period.

6.2.8 Diet Monitoring

The diets of patients enrolled in the study will be monitored as follows:

1. All patients will be required to maintain a 7-day food diary prior to Week 1, Week 13, Week 26, Week 52, and Week 65.

2. Patients will receive diet/alcohol counseling by qualified study personnel at clinic visits throughout the course of the study. Qualified study personnel will telephone the patient to provide diet/alcohol counseling for visits that are conducted by a clinical service.

3. In addition to the 7-day food diary and the diet /alcohol counseling during clinic visits, telephone calls from a dietitian or qualified study personnel to assess as to how each patient is maintaining their diet will be conducted randomly during the treatment and post treatment follow-up periods.

6.2.9 Family History

Family history of hypertriglyceridemia and pancreatitis will be collected for each patient.

6.2.10 Lipoprotein Lipase Activity Sample Collection

Lipoprotein lipase (LPL) activity will be measured in ISIS 304801-CS16 rollover patients if needed for study qualification. In brief, fasted patients will be given a low intravenous dose of heparin. A blood sample will be drawn prior to and at 10 or 15 minutes after the heparin administration for measurement of LPL activity as per instructions provided to the Investigator.

6.3 Restriction on the Lifestyle of Patients

6.3.1 Contraception Requirements

All male patients and women of childbearing potential must refrain from sperm/egg donation and either be abstinent* or, if engaged in sexual relations of child-bearing potential, practice effective contraception from the time of signing the informed consent form until at least 13 weeks after their last dose of study treatment.

Male patients must also encourage their female partner to use effective contraception from the time of signing the informed consent until 13 weeks after the subject's last dose of study treatment.

For the purposes of this Study, women of childbearing potential are defined as any female who has experienced menarche, and who does not meet 1 of the following conditions:

- Postmenopausal: 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved
- 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Post hysterectomy

For the purposes of the study, effective contraception is defined as follows:

For male patients:

- Effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the use of condoms together with spermicidal foam/gel/film/ cream/suppository. Male patients must also encourage their female partner to use effective contraception from the time of signing the informed consent until 3 months after the patient's last dose of study treatment. Effective contraceptive for the female partner includes: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or barrier methods (female condom*, diaphragm, sponge, cervical cap) together with spermicidal foam/gel/film/cream/suppository. Male patients with partners that are pregnant must use condoms to ensure that the fetus is not exposed to the Study Drug.

For female patients:

- Using one or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine

contraception/device, or any 2 barrier methods (a combination of male or female condom* with diaphragm, sponge, or cervical cap) together with spermicidal foam/gel/film/cream/suppository.

*Note: A female condom and a male condom should not be used together as friction between the two can result in either product failing.

* Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception

6.3.2 Other Requirements

All patients will be required to fast for at least 10 hours and preferably not more than 12 hours before visits requiring fasted blood sampling.

All patients will be encouraged to follow a diet comprising ≤ 20 g fat per day during the study.

Alcohol should not be consumed during the study.

All patients will be given an instruction card that must be presented to the treating physician if a suspected case of pancreatitis occurs. The card will explain that the patient is in a clinical trial and that serum lipase and/or amylase measures should be done in order to adjudicate the event, based on Atlanta Classification (Banks et al. 2013). If serum or amylase activity is less than 3 x upper limit of normal (ULN), imaging, preferably contrast-enhanced computed tomography, should be considered to confirm the diagnosis of acute pancreatitis per the Atlanta Criteria.

7. STUDY DRUG

7.1 Volanesorsen Description

Volanesorsen drug product (ISIS 304801) characteristics are listed in Table 1.

Volanesorsen (ISIS 304801) is contained in glass prefilled syringes (PFS). Volanesorsen and its storage and preparation instructions will be provided by the Sponsor or designee. Volanesorsen must be stored securely at 2° to 8° C and be protected from light.

Table 1 Volanesorsen (ISIS 304801) Characteristics

Strength	200 mg/mL
Volume/Formulation	1.5 mL solution per PFS
Dose	300 mg once weekly
Route of Administration	SC

7.2 Packaging and Labeling

The Sponsor will provide the Investigator with packaged volanesorsen labeled (ISIS 304801) in accordance with specific country regulatory requirements.

7.3 Study Drug Accountability

The study staff is required to document the receipt, dispensing, and return/destruction of volanesorsen provided by the Sponsor. The Study Center must return all unused volanesorsen to the Sponsor or designee. All used syringes must be disposed of as per the site's hazardous waste destruction policy.

8. TREATMENT OF PATIENTS

8.1 Volanesorsen Administration

For each individual patient, volanesorsen will be administered subcutaneously as a single 1.5 mL injection once weekly for Weeks 1-52.

Patients should receive 1 dose per week, with weeks always defined relative to Study Day 1. For example if a patient receives the first dose on a Monday, subsequent doses should be given on Mondays, if possible. If a patient misses an injection, or if dosing on the usual day is not possible, the patient can reschedule the injection provided that 2 doses are administered at least 2 days apart.

Every effort should be made to ensure the previous week's dose is given 7 days prior to a scheduled clinic visit.

Please refer to the Study Drug Manual provided by the Sponsor for more detailed instructions for volanesorsen preparation and administration.

8.2 Other Protocol-Required Drugs

There are no other protocol-required drugs (Section 6.2.5).

8.3 Other Protocol-Required Treatment Procedures

There are no other protocol required treatment procedures for this study.

8.4 Treatment Precautions

There are no specific treatment precautions required for this study.

8.5 Safety Monitoring Rules

Please refer also to the 'Guidance for Investigator' section of the Investigator's Brochure.

For the purposes of safety monitoring baseline is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 (e.g., qualification assessments or assessments from the final visits of ISIS 304801-CS6 and ISIS 304801-CS16 index studies if used for qualification).

In addition to the standard monitoring of clinical safety parameters, the following guidelines are provided for the monitoring of selected parameters chosen based on preclinical and clinical observations.

Confirmation Guidance: At any time during the study (Treatment or Post-Treatment Periods), the initial clinical laboratory results meeting the safety monitoring or stopping criteria presented below **must be confirmed** by performing measurements (ideally in the same laboratory that performed the initial measurement) on new specimens. All new specimen collections should take place as soon as possible (ideally within 3 days of the initial collection). For stopping rules, if the initial laboratory result is observed during the Treatment Period, the results from the retest **must be available** prior to administering the next dose of volanesorsen.

In addition to the safety monitoring parameters listed below, the Sponsor may request confirmation of additional lab values.

Re-dosing Guidance: Patients with initial laboratory test values that reach a stopping rule must not be re-dosed until the re-test results are available. In general, patients who do not meet the stopping rules based upon retest may continue dosing. However, the Investigator and the Sponsor Medical Monitor (or appropriately qualified designee) should confer as to whether additional close monitoring of the patient is appropriate. If any of the stopping criteria described below (refer to Sections 8.6.1 to 8.6.3) are met, the patient will be permanently discontinued from further treatment with volanesorsen, evaluated fully as outlined below and in consultation with the Sponsor Medical Monitor or appropriately qualified designee, and will be followed up in accordance with Section 8.8 of the protocol.

8.5.1 Safety Monitoring for Liver Chemistry Tests

The following rules are adapted from the draft guidance for industry, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," issued by the U.S. Department of Health and Human Services, Food and Drug Administration, July 2009. For a definition of Baseline please refer to guidance in Section 8.5 above.

In the event of an ALT or AST measurement that is > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) at any time during the study (Treatment or Post-Treatment Period), the initial measurement(s) should be confirmed as described above. Additional confirmatory measurements should also be performed if ALT or AST levels increase to 5 x ULN.

Frequency of Repeat Measurements: Patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) should have their liver chemistry tests (ALT, AST, alkaline phosphatase (ALP), international normalized ratio

(INR) and total bilirubin) retested at least once-weekly until ALT and AST levels become ≤ 1.2 x ULN or 1.2 x baseline value if the baseline value was > ULN.

Further Investigation into Liver Chemistry Elevations: For patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), the following evaluations should be performed:

1. Obtain a more detailed history of symptoms and prior and concurrent diseases
2. Obtain further history for concomitant drug use (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
3. Obtain a history for exposure to environmental chemical agents and travel
4. Serology for viral hepatitis (HAV IgM, HBsAg, HCV antibody, CMV IgM, and EBV antibody panel)
5. Serology for autoimmune hepatitis (e.g., antinuclear antibody [ANA])

Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic CT or MRI scans, may be performed at the discretion of the Investigator, in consultation with the Sponsor Medical Monitor. Repetition of the above evaluations should be considered if a patient's ALT and/or AST levels reach 5 x ULN.

8.5.2 Safety Monitoring for Platelet Count Results

In the event of any significant fall in platelet count, or if the absolute platelet count is 75,000/mm^3 or less, then the patient's platelet counts should be monitored more frequently. The frequency of monitoring and additional lab tests will be determined by the Sponsor Medical Monitor or designee in consultation with the Investigator.

Any case of a platelet count ≤ 50,000/mm^3 should be reported in an expedited fashion to the Sponsor (See also Stopping Rules Section 8.6.3).

8.5.3 Safety Monitoring for Minor Bleeding Events

Minor bleeding events are those that do not fulfill the criteria for major bleeding or clinically-relevant, non-major bleeding events (which are defined in Section 8.6.3), for example excess bruising, petechiae, gingival bleeding on brushing teeth. If a minor bleeding event occurs, the Investigator must notify the Sponsor Medical Monitor and additional testing of coagulation parameters activated partial thromboplastin time (aPTT), prothrombin time (PT), INR and platelet count should be performed.

8.5.4 Safety Monitoring for Constitutional Symptoms

Patients will be instructed to promptly report any signs of symptoms of fever or constitutional symptoms that may arise during the study and the Investigator should closely evaluate all potential causes, including concomitant illness. Patients that experience persistent constitutional symptoms should be discussed with the Sponsor Medical Monitor or designee to determine whether additional monitoring or laboratory tests are required.

8.5.5 Safety Monitoring for LDL-C Elevations

Beginning at Week 13, laboratory alerts will be in place to notify the Investigator if a patient has a low-density lipoprotein-cholesterol (LDL-C) > 160 mg/dL (> 130 mg/dL for patients with T2DM) on 2 consecutive visits. If this occurs, LDL-C values for this patient will be unblinded for the remainder of the study and the Investigator will be encouraged to initiate/adjust treatment to lower LDL-C according to country-specific guidelines (e.g., initiate statin therapy or increase the statin dose for patients who are already on treatment).

8.5.6 Safety Monitoring for Insulin, Oral Antidiabetic Medication and Glucose

All patients on insulin will monitor their glucose levels with a glucometer as per standard practice guidelines and bring their glucometer or glucometer log printout to every clinic visit. In addition, patients who are not on insulin but use a glucometer should also bring their glucometer and/or glucometer log printout to every clinic visit.

- The Investigator or delegate will review the glucometer reading or printout at every clinic visit to evaluate if fasting pre-breakfast self-monitored plasma glucose values exceed threshold values as per the Safety Monitoring Rules for Hyperglycemia below.

All diabetic patients will note any changes in their insulin dose and /or oral antidiabetic therapy, as well as any hypoglycemic episode they may experience.

- The Investigator or delegate will ask patients at every clinic visit if they made changes in their insulin dose or oral antidiabetic therapy, and if they experienced a hypoglycemic episode.
  - Patients will be instructed on the monitoring and management of hypoglycemic episodes at each visit.
  - Documented symptomatic hypoglycemic episodes should be captured as adverse events in the adverse event CRF. Documented symptomatic hypoglycemia is defined as typical hypoglycemia symptoms accompanied by measured plasma glucose ≤ 70 mg/dL (≤ 3.9 mmol/L).
  - Any changes in insulin dose or oral antidiabetic therapy should be captured into the Concomitant Medication CRF.

8.5.7 Safety Monitoring for Documented Severe Hypoglycemia

A **documented severe hypoglycemic event** is defined as 1 in which the patient requires assistance of another person to obtain treatment for the event and has a plasma glucose level ≤ 70 mg/dL (≤ 3.9 mmol/L). The rescue treatment of hypoglycemia may include IV glucose or buccal or intramuscular glucagon.

The definition of severe symptomatic hypoglycemia includes all episodes in which neurological impairment was severe enough to prevent self-treatment and which were thus thought to place patients at risk for injury to themselves or others. Note that “requires assistance” means that the patient could not help himself or herself. Someone being kind that assists spontaneously the patient when not necessary does not qualify as “requires assistance.”

Severe hypoglycemia will be qualified as a SAE only if it fulfills SAE criteria.

If a patient presents with symptoms of hypoglycemia, the Investigator will need to take immediate action to confirm the patient's glucose level and treat the patient accordingly.

The experience of hypoglycemia may vary greatly from patient to patient. However, there are certain classical signs and symptoms, of which patients should be aware as a clue that their blood glucose may be low. Common symptoms include headache, heart pounding, confusion, disorientation, numbness or tingling, pale skin, shakiness or tremulousness, increased appetite, anxiousness or nervousness, lightheadedness or dizziness, sweating, and weakness. Coma could occur if blood sugar correction is not performed.

If patients suspect they might be having a hypoglycemia reaction, they should check their blood glucose using their meters as soon as possible, before treatment if possible, provided they feel it is safe to do so. If there is doubt about safety they should treat the event first, using some sugar, milk, or juice for example, then obtain and record a blood glucose value as soon as possible thereafter. The time and nature of treatment should be noted, and especially if any blood glucose result was before or after treatment. It would be helpful for the patient to note if a contributory factor (e.g., missed or reduced meals, unaccustomed physical activity) occurred earlier in the day of the event.

8.5.8 Safety Monitoring for Hyperglycemia

Upward dose titration and/or addition of any other anti-hyperglycemic agent(s) will not be allowed during the course of the study, unless specific threshold values are met at Week 13 or later and confirmed on subsequent testing (ideally within 1 week of the initial test).

HbA1c is monitored every 3 months throughout the study. In addition, patients on insulin should self-monitor their plasma glucose (SMPG) routinely on a glucometer as per practice guidelines. If a fasting pre-breakfast SMPG value exceeds the specific glycemic limit, the patient should check it again on the following 2 days. If all the fasting pre-breakfast values on 3 consecutive days exceed the specific limit, the patient should contact the Investigator and an unscheduled central laboratory FPG measurement and HbA1c should be performed.

The threshold values are defined as:

- FPG > 270 mg/dL (15.0 mmol/L)
- HbA1c > 9% (for patients with baseline HbA1c < 8% and HbA1c increase of more than 1% from baseline (for patients with baseline HbA1c ≥ 8 and < 9%)

In case of confirmed FPG/HbA1c above the threshold value, the Investigator should ensure that no reasonable explanation exists for insufficient glucose control and in particular that:

- Plasma glucose was actually measured in the fasting condition (i.e., after at least 10 hours fast)
- Absence of intercurrent disease which may jeopardize glycemic control. In case of an emergency (e.g., surgery, infection), the Investigator can take appropriate measures for glycemic control
- Compliance to treatment is appropriate

- Compliance to diet and lifestyle is appropriate

If any of the above can reasonably explain the insufficient glycemic control, the Investigator should consider the following:

- Investigation and treatment of intercurrent disease (to be reported in adverse event (AE)/concomitant medication parts of the e-CRF)
- Stress on the absolute need to be compliant to treatment
- Organize a specific interview with a Registered Dietician or other qualified nutrition professional and stress on the absolute need to be compliant to diet and lifestyle recommendations

A FPG/HbA1c follow-up assessment should be arranged after appropriate action has been taken. If none from the above-mentioned reasons can be found, or if appropriate action fails to decrease FPG/HbA1c under the threshold values, additional medication may be introduced at the Investigator's discretion and according to local guidelines after discussion with the Sponsor Medical Monitor.

8.5.9 Acute Pancreatitis

If a patient has an episode of acute pancreatitis, dosing with Study Drug should be suspended temporarily until the patient is clinically stable. The suitability of the patient for continued dosing and the need for any modification to treatment schedule (refer to Section 8.7) will be determined by the Investigator in consultation with the Study Medical Monitor.

8.6 Stopping Rules

For the purposes of stopping rules baseline is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1.

8.6.1 Stopping Rules for Liver Chemistry Elevations

In the event of laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor,** dosing of a patient with volanesorsen will be stopped permanently; values that are not confirmed due to failure to retest or missing lab values will be presumed confirmed:

1. ALT or AST > 8 x ULN, which is confirmed
2. ALT or AST > 5 x ULN, which is confirmed and persists for ≥ 2 weeks
3. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed **and** total bilirubin > 2 x ULN or INR > 1.5
4. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed, and the new appearance (i.e., onset coincides with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> ULN) felt by the Investigator to be potentially related to hepatic inflammation

8.6.2 Stopping Rules for Renal Function Test Results

In the event of a persistent elevation that is observed over 2 consecutive weeks, for any of the 3 criteria below, dosing of a patient with volanesorsen may be stopped temporarily:

1. Serum creatinine increase that fulfill all of the following criteria: ≥ 0.3 mg/dL (26.5 µmol/L) and ≥ 40% above baseline creatinine values and > ULN

2. Proteinuria, dipstick 2 + (confirmed by dipstick retest and then further confirmed by a quantitative total urine protein measurement of > 1.0 g/24-hour)

3. Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault ≤ 40 mL/min that is confirmed by a 24-hour urine collection

The possible dosing re-initiation or follow-up schedule for any events meeting either of these criteria will be determined by the Investigator **in consultation with** the Sponsor Medical Monitor or designee.

8.6.3 Stopping Rules for Platelet Count Results

In the event of a platelet count less than 50,000/mm^3 that is associated with major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with volanesorsen will be stopped permanently. The follow-up schedule for any events meeting this stopping criterion will be determined by the Investigator in consultation with the Sponsor Medical Monitor.

In the event of a platelet count less than 50,000/mm^3, and in the absence of major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with volanesorsen should be suspended temporarily until the platelet count has recovered to ≥ 100,000/mm^3. The suitability of the patient for continued dosing and the need for any modification to treatment schedule (refer to Section 8.7) will be determined by the Investigator in consultation with the Study Medical Monitor and will be based on factors such as the original rate of decline in the patient's platelet count, whether any bleeding events were experienced by the patient, and the speed of recovery of platelet count upon holding of dosing.

If after the first dosing rechallenge the platelet count again falls below 50,000/mm^3, then dosing of the patient must be held until the platelet count again returns to at least 100,000/mm^3. The suitability of the patient for continued dosing and the need for any further modification to treatment schedule or dose (refer to Section 8.7) will be re-examined by the Investigator in consultation with the Study Medical Monitor based on (at least) the factors mentioned above.

If after the second rechallenge the platelet count falls below 50,000/mm^3 and is subsequently confirmed (see Section 8.5), dosing with volanesorsen will be stopped permanently. The follow-up schedule for any events meeting this stopping criterion will be determined by the Investigator in consultation with the Study Medical Monitor.

Following a rechallenge platelet count should be tested every week until count is stable.

Any unreportable platelet count result must be rechecked and determined not to have met a stopping rule before dosing can continue.

Definition of Major Bleeding Events (Schulman et al. 2005):

- Fatal bleeding, and/or
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarterial or pericardial, or intramuscular with compartment syndrome, and/or
- Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more within 24 hours, or leading to transfusion of 2 or more units of whole or red cells

Definition of Clinically-Relevant, Non-Major Bleeding Events (Schulman et al. 2005):

1. Multiple-source bleeding
2. Spontaneous hematoma > 25 cm^2
3. Excessive wound hematoma (not injection site related)
4. Macroscopic hematuria (spontaneous or lasting > 24 hours if associated with an intervention)
5. Spontaneous rectal bleeding; epitasis, gingival bleeding, hemoptysis, hematemesis
6. Bleeding after venipuncture for > 5 minutes

8.7 Adjustment of Dose Frequency

Dose adjustments, including dose interruptions, and/or decreasing the dose frequency will be allowed for safety and tolerability. Any proposed adjustment to treatment schedule must be discussed with, and approved by, the Study Medical Monitor prior to initiation. Up to 2 adjustments in the treatment schedule may be allowed for patients that are unable to tolerate the once weekly dose (for example if platelet counts fall below 50,000/mm^3 as described in Section 8.6.3). If the patient remains stable after adjustment, they may be cautiously returned to the original once weekly regimen after consultation with the Study Medical Monitor.

Patients may be dose paused in response to AEs after consultation with Study Medical Monitor.

8.8 Discontinuation of Study Treatment

A patient must permanently discontinue study treatment for any of the following:

- The patient becomes pregnant. Report the pregnancy according to instructions in Section 9.5.4
- The patient withdraws consent
- The patient experiences an AE that necessitates permanent discontinuation of study treatment

- The patient develops laboratory test abnormalities that meet any of the stopping rules listed in Section 8.6

The reason for discontinuation of study treatment must be recorded in the CRF and source documentation.

8.8.1 Follow-up Visits for Early Termination from Treatment Period

Any patient who discontinues early from the Treatment Period should be strongly encouraged to attend applicable landmark visits at Weeks 12, 13, 25, 26, and 51, 52 (calculated based on the time elapsed since Day 1) to collect fasting lipid panels and conduct safety assessments in accordance with the schedule of procedures in Appendix A. Any patient who discontinues treatment after Week 44 should also be strongly encouraged to attend a final follow-up visit (Week 65 visit assessments) approximately 13 weeks after their last dose of Study Drug, in addition to the applicable landmark visits.

If the patient declines or is unable to participate in the above, an early termination (ET) visit (Week 52 visit assessments) should be performed at the time of withdrawal, at a minimum, and ideally within 2 weeks from the last dose of Study Drug.

8.8.2 Follow-up Visits for Early Termination from Post-Treatment Follow-up Period

The patient who requests to withdraw from the study during the Post-Treatment Follow-up Period should be encouraged to undergo a final follow-up visit (Week 65, see Appendix A) prior to leaving the study.

If a patient withdraws due to an AE at any time during the study, the Investigator should arrange for the patient to have appropriate follow-up until the AE has resolved or stabilized.

8.9 Withdrawal of Patients from the Study

Patients must be withdrawn from the study for any of the following:

- Withdrawal of consent
- The patient is unwilling or unable to comply with the protocol

Other reasons for withdrawal of patients from the study might include:

- At the discretion of the Investigator for medical reasons
- At the discretion of the Investigator or Sponsor for noncompliance
- Significant protocol deviation

All efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information, including the reason for withdrawal from study, must be recorded in the CRF.

Any patient who withdraws consent to participate in the study will be removed from further treatment and study observation immediately upon the date of request. These patients should be

encouraged to complete the ET study procedures and observations at the time of withdrawal (see Section 8.8 and Appendix A).

For patients withdrawn for reasons other than withdrawal of consent every effort should be made to complete the early termination study procedures and observations at the time of withdrawal (see Section 8.8 and Appendix A).

8.10 Concomitant Therapy and Procedures

The use of concomitant therapies or procedures defined below must be recorded on the patient's CRF. AEs related to administration of these therapies or procedures must also be documented on the appropriate CRF.

8.10.1 Concomitant Therapy

A concomitant therapy is any non-protocol specified drug or substance (including over-the-counter medications, herbal medications and vitamin supplements) administered between signing informed consent and completion of the post-treatment follow-up period. All concomitant medications/treatments and significant non-drug therapies (including supplements and assistive devices) received by a patient, including changes in the patient's current medications, must be recorded in the patient's source documents and CRF. Patients taking over the counter (OTC) omega-3 fatty acids should make every effort to remain on the same brand throughout the study.

Allowed Concomitant Therapy

Any medications deemed necessary by the Investigator are allowed except those listed in the disallowed concomitant therapy.

Disallowed Concomitant Therapy

No lipid lowering therapies (e.g., fibrates, niacin, fish oil or other products containing omega-3 fatty acids [including OTC preparations]), -glucagon-like peptide-1 (GLP-1) agonists, Glybera, or systemic corticosteroids may be started or adjusted after baseline qualification. Doses of existing oral anti-diabetic medication, oral contraceptives, hormone replacement therapy, anticoagulants, or drugs or dietary supplements with potential lipid-altering effects should not be adjusted. Study patients are prohibited from receiving other experimental agents during the study. This includes marketed agents at experimental dosages that are being tested for the treatment of hypertriglyceridemia.

Patients should consult with the Site Investigator or designee prior to initiating any new medication, including non-prescription or herbal compounds or any other non-drug therapy.

8.10.2 Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between signing of informed consent and Week 65 visit.

Disallowed Concomitant Procedure

Plasma apheresis is not allowed during the study.

8.11 Treatment Compliance

Compliance with treatment dosing is to be monitored and recorded by Study Center staff. The Study Center staff is required to document the receipt, dispensing, and return/destruction of volanesorsen. Patients that are self-administering volanesorsen at home must record treatment in a dosing diary that will be reviewed periodically by Study Center staff and the Clinical Monitor.

9. SERIOUS AND NON-SERIOUS ADVERSE EVENT REPORTING

9.1 Sponsor Review of Safety Information

Safety information will be collected, reviewed, and evaluated by the Sponsor in accordance with the Safety Management Plan throughout the conduct of the clinical trial.

9.2 Regulatory Requirements

The Sponsor is responsible for regulatory submissions and reporting to the Investigators of serious adverse events (SAEs) including suspected unexpected serious adverse reactions (SUSARs) per the International Conference on Harmonization (ICH) guidelines E2A and ICH E6. Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines.

Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) will be notified of any SAE according to applicable regulations. The Independent DSMB will be notified of any SAE as specified in the DSMB charter.

In addition to the Investigator's assessment of relatedness, the Sponsor or designee will evaluate the available information and perform an independent assessment of relatedness. While the Sponsor may upgrade an Investigator's decision it is not permissible to downgrade the Investigator's opinion for the purposes of determining whether the SAE meets the definition of a SUSAR.

The following table identifies the SAEs that the Sponsor or designee will not report on an individual basis in an expedited manner because they are anticipated to occur in the study population independent of volanesorsen exposure. The Investigator still has the responsibility to report all SAEs to the Sponsor as described in Sections 9.4.1 to 9.4.3.5.

Table 2 Expected Event for the Protocol Defined Population by Preferred Term and the Expected Incidence

Preferred Term	Expected Incidence in the Protocol Defined Population (Gaudet et al. 2010 and 2013)
Pancreatitis associated events including the PTs of hereditary pancreatitis, pancreatitis, pancreatitis acute, pancreatitis chronic, pancreatitis necrotizing, pancreatitis relapsing	0.2-0.35 events per patient-year

Fatal pancreatitis associated events will be considered as unexpected and are reportable. The Sponsor and DSMB will monitor non-fatal pancreatitis associated SAEs using the incidence rate of the event compared to the rate expected in a non-volanesorsen exposed population. If the

aggregate analysis indicates that an event is occurring significantly more frequently or at a greater severity than expected, then the event will be reported.

SAEs not specified in the table will be evaluated on case by case basis to determine whether there is a reasonable possibility that the drug caused the event. If the event is considered by the Sponsor or designee to meet the definition of a SUSAR the event will be reported.

9.3 Definitions

9.3.1 Adverse Event

An adverse event is any unfavorable and unintended sign (including a clinically-significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the study or use of investigational drug product, whether or not the AE is considered related to the investigational drug product.

9.3.2 Adverse Reaction and Suspected Adverse Reaction

An adverse reaction is any adverse event caused by volanesorsen.

A suspected adverse reaction is any adverse event for which there is a reasonable possibility that volanesorsen drug caused the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

9.3.3 Serious Adverse Event (SAE)

A serious adverse event is any adverse event that in the view of either the Investigator or Sponsor, meets any of the following criteria:

- Results in death
- Is life threatening: that is, poses an immediate risk of death at the time of the event

An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Hospitalization is defined as an admission of greater than 24 hours to a medical facility and does not always qualify as an AE
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly or birth defect in the offspring of the patient (whether the patient is male or female)
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered serious when, based upon appropriate

medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

9.4 Monitoring and Recording Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the study (i.e., before informed consent) should be recorded as Medical History and not recorded as AEs unless the pre-existing condition worsened. The Investigator should always group signs and symptoms into a single term that constitutes a **single unifying diagnosis** if possible.

9.4.1 Serious Adverse Events

In the interest of patient safety, and in order to fulfill regulatory requirements**,** all SAEs (regardless of their relationship to volanesorsen) should be reported to the Sponsor or designee within 24 hours of the Study Center's first knowledge of the event. The collection of SAEs will begin after the patient signs the informed consent form and stop at the end of the patient's follow-up period which is defined as the Week 65 visit. When the Investigator is reporting by telephone, it is important to speak to someone in person versus leaving a message. An Initial Serious Adverse Event Form should be completed and a copy should be faxed to the Sponsor or designee.

Detailed information should be actively sought and included on Follow-Up Serious Adverse Event Forms as soon as additional information becomes available. All SAEs will be followed until resolution. SAEs that remain ongoing past the patient's last protocol-specified follow-up visit will be evaluated by the Investigator and Sponsor. If the Investigator and Sponsor agree the patient's condition is unlikely to resolve, the Investigator and Sponsor will determine the follow-up requirement.

9.4.2 Non-Serious Adverse Events

The recording of non-serious AEs will begin after the patient signs the informed consent form and will stop at the end of the patient's follow-up period, which is defined as the Week 65 visit. The Investigator will monitor each patient closely and record all observed or volunteered AEs on the Adverse Event Case Report Form.

9.4.3 Evaluation of Adverse Events (Serious and Non-Serious)

The Investigator's opinion of the following should be documented on the Adverse Event Case Report Form:

9.4.3.1 Relationship to the Study Drug

The event's relationship to volanesorsen is characterized by 1 of the following:

- **Related:** There is clear evidence that the event is related to the use of volanesorsen e.g., confirmation by positive rechallenge test

- **Possible:** The event cannot be explained by the patient's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and volanesorsen administration

- **Unlikely/Remote:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to volanesorsen administration and/or exposure suggests that a causal relationship is unlikely (For reporting purposes, Unlikely/Remote will be grouped together with Not Related)

- **Not Related:** The event can be readily explained by the patient's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and volanesorsen

9.4.3.2 Severity

The severity of AEs and SAEs will be graded based on criteria from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010 (refer to Appendix D). Any AE not listed in Appendix D will be graded as follows:

- **Mild:** The event is easily tolerated by the patient and does not affect the patient's usual daily activities

- **Moderate:** The event causes the patient more discomfort and interrupts the patient's usual daily activities

- **Severe:** The event is incapacitating and causes considerable interference with the patient's usual daily activities

If the event is an SAE, then all applicable seriousness criteria must be indicated (criteria listed in Section 9.3.3).

9.4.3.3 Action Taken with Volanesorsen

Action taken with volanesorsen due to the event is characterized by 1 of the following:

- **None:** No changes were made to volanesorsen administration and dose

- **Permanently Discontinued:** Volanesorsen was discontinued and not restarted

- **Temporarily Interrupted, restarted – same dose:** Dosing was temporarily interrupted or delayed due to the AE and restarted at the same dose

- **Reduced schedule:** Dosing frequency was reduced

9.4.3.4 Treatment Given for Adverse Event

Any treatment (e.g., medications or procedures) given for the AE should be recorded on the Adverse Event Case Report Form (treatment should also be recorded on the concomitant treatment or ancillary procedures CRF as appropriate).

9.4.3.5 Outcome of the Adverse Event

If the event is a non-serious AE then the event's outcome is characterized by 1 of the following:

- **AE Persists:** Patient terminates from the trial and the AE continues
- **Recovered:** Patient recovered completely from the AE
- **Became Serious:** The event became serious (the date that the event became serious should be recorded as the Resolution Date of that AE and the Onset Date of the corresponding SAE)
- **Change in Severity** (if applicable): AE severity changed

If the event is a SAE then the event's outcome is characterized by 1 of the following:

- **Ongoing:** SAE continuing
- **Persists (as non-serious AE):** Patient has not fully recovered but the event no longer meets serious criteria and should be captured as an AE on the non-serious AE eCRF (the SAE resolution date should be entered as the date of onset of that AE)
- **Recovered:** Patient recovered completely from the SAE (the date of recovery should be entered as the SAE resolution date)
- **Fatal:** Patient died (the date of death should be entered as the SAE resolution date)

9.4.4 Adjudication Committees

All SAEs that occur during the study that are consistent with a major acute cardiovascular event (MACE) will be adjudicated by a blinded, independent committee as outlined in the MACE Adjudication Charter.

All AEs and SAEs that occur during the study that are consistent with an event of acute pancreatitis will be adjudicated by a blinded, independent committee according to the Atlanta classification of acute pancreatitis (Banks et al. 2013) and as outlined in the Pancreatitis Adjudication Charter. In addition, data for prior episodes of acute pancreatitis or suspected pancreatitis will be collected by review of each patient's medical chart and these events will also be adjudicated.

9.5 Procedures for Handling Special Situations

9.5.1 Abnormalities of Laboratory Tests

Clinically-significant abnormal laboratory test results may, in the opinion of the Investigator, constitute or be associated with an AE. Examples of these include abnormal laboratory results that are associated with symptoms, or require treatment, e.g., bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac arrhythmias due to hyperkalemia. Whenever possible, the underlying diagnosis should be listed in preference to abnormal laboratory values as AEs. Clinically-significant abnormalities will be monitored by the Investigator until the parameter returns to its baseline value or until agreement is reached between the Investigator and Sponsor

Medical Monitor. Laboratory abnormalities deemed not clinically-significant (NCS) by the Investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator should not be deemed NCS on the laboratory sheet.

The Investigator is responsible for reviewing and signing all laboratory reports. The signed clinical laboratory reports will serve as source documents and should include the Investigator's assessment of clinical significance of out of range/abnormal laboratory values.

9.5.2 Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the patient is hospitalized; the Study Center must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the patient's consent to participate in the study
- The condition that required the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the patient's consent to participate in the study and the timing of the procedure or treatment
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission

9.5.3 Dosing Errors

Volanesorsen dosing errors should be documented as Protocol Deviations. A brief description should be provided in the deviation, including whether the patient was symptomatic (list symptoms) or asymptomatic, and the event accidental or intentional.

Dosing details should be captured on the Dosing Case Report Form. If the patient takes a dose of volanesorsen that exceeds protocol specifications and the patient is symptomatic, then the symptom(s) should be documented as an AE and be reported per Section 9.4.

Should an overdose occur, the Investigator or designee should refer to the Guidance to Investigator's section of the Investigator's Brochure and contact the Sponsor or designee within 24 hours.

9.5.4 Contraception and Pregnancy

Male patients and female patients of childbearing potential must continue to use appropriate contraception with their partners, or refrain from sexual activity, as described in Section 6.3.1.

If a patient becomes pregnant or a pregnancy is suspected, or if a male patient makes or believes that he has made someone pregnant during the study, then the Study Center staff must be informed immediately. An Initial Pregnancy Form should be submitted to the Sponsor or designee **within 24 hours** of first learning of the occurrence of pregnancy. Follow-up information including delivery or termination is reported on Follow-up Pregnancy Forms and reported within 24 hours.

Payment for all aspects of obstetrical care, child or related care will be the patient's responsibility.

Female patients: If a suspected pregnancy occurs while on the study (including follow-up), a pregnancy test will be performed. The patient with a confirmed pregnancy will be immediately withdrawn from treatment with volanesorsen. However, the patient will be encouraged to complete the post-treatment follow-up portion of the study to the extent that study procedures do not interfere with the pregnancy. Regardless of continued study participation, the study physician will assist the patient in getting obstetrical care and the progress of the pregnancy will be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the Study Center and Sponsor may require access to the mother and infant's medical records for an additional 8 weeks after birth.

Male patients: The progress of the pregnancy in a male patient's partner should be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, **the Study Center and Sponsor may request access to the mother and infant's medical records for an additional 8 weeks after birth**. Follow-up will be performed to the extent permitted by applicable regulations and privacy considerations.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints

For fasting lipid measurements, the values at Month 3 analysis time point are defined as the average of Week 12 (Day 78) and Week 13 (Day 85) fasting assessments, the values of Month 6 analysis time point is at the end of Month 6 are defined as the average of Week 25 (Day 169) and Week 26 (Day 176) fasting assessments, and the values at the Month 12 analysis time point are defined as the average of Week 51 (Day 351) and Week 52 (Day 358) fasting assessments.

10.1.1 Efficacy Endpoints

- Percent change and absolute change from baseline in fasting TG
- Frequency and severity of patient reported abdominal pain during the treatment period
- Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-HDL-C, apoB, HDL-C, apolipoprotein A-1 (apoA-1), VLDL-C, and LDL-C
- Percent change from baseline in fasting total apolipoprotein C-III
- Quality of Life questionnaires (EQ-5D, SF-36)
- Adjudicated acute pancreatitis event rate
- Other symptoms: eruptive xanthoma, lipemia retinalis

10.1.2 Safety Endpoints

- Adverse events including adjudicated events of pancreatitis and MACE
- Vital signs and weight
- Physical examinations
- Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis)
- Echocardiography
- Electrocardiograms (ECGs)
- Use of concomitant medications
- MRIs

10.2 Sample Size

No sample size calculations were performed as this is an extension study to the double-blind, placebo-controlled ISIS 304801-CS6 and ISIS 304801-CS16 studies. Approximately 70 patients may be eligible to enroll into this study.

10.3 Populations

Full Analysis Set (FAS): All patients who are enrolled and have a baseline TG assessment. The FAS represents the practically-feasible intent-to-treat (ITT) population as delineated in ICH Guideline E9.

Per Protocol Set (PPS): Subset of the FAS who received 9 of first 13 scheduled doses of volanesorsen and with no significant protocol deviations that would be expected to affect efficacy and PD assessments. The detailed criteria will be specified and finalized prior to the final database lock.

Safety Set: All patients who are enrolled and receive at least 1 dose of volanesorsen.

PK Population: All patients who are enrolled, receive at least 1 dose of volanesorsen, and have at least 1 evaluable PK sample collected, analyzed, and reported.

10.4 Definition of Baseline

Definitions of baseline are given below for the purposes of the final analysis.

For fasting lipid measurements, 2 baselines are defined for each patient: ISIS 304801-CS6 or ISIS 304801-CS16 index study baseline and the baseline in this open label study, which is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 (e.g., qualification assessments or assessments from final visit of the ISIS 304801-CS6 or ISIS 304801-CS16 index studies if used for qualification).

For other measurements, baseline for patients on active treatment in the ISIS 304801-CS6 or ISIS 304801-CS16 index study will be the ISIS 304801-CS6 or ISIS 304801-CS16 index study

baseline. For patients on placebo in the ISIS 304801-CS6 or ISIS 304801-CS16 index study, baseline for safety will be the last non-missing assessment prior to the first dose of Study Drug.

10.5 Interim Analysis

An interim analysis may be conducted after the last patient's Week 13 visit of the extension study or after the database of the ISIS 304801-CS6 and ISIS 304801-CS16 index studies are locked and unblinded. Both safety and efficacy information from this OLE study may be summarized during this interim analysis. Efficacy analyses will be detailed in the SAP.

10.6 Planned Methods of Analysis

All eCRF data, lab data transfers, as well as any outcomes derived from the data, will be provided in the patient data listings. Patient data listings will be presented for all patients enrolled into the study. Descriptive summary statistics including n, mean, median, standard deviation, standard error, interquartile range (25th percentile, 75th percentile), and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data by treatment group. Where appropriate, p-values will be reported. All statistical tests will be conducted using 2-sided tests with 5% Type I error rates unless otherwise stated.

All efficacy endpoints will be assessed in the FAS and PPS. All safety assessments will be performed on the Safety Set. PK endpoints will be assessed in the PK Set as applicable.

10.6.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics by treatment group. The patient disposition will be summarized by treatment group of the index studies. All patients enrolled will be included in a summary of patient disposition.

10.6.2 Safety Analysis

Treatment duration and amount of Study Drug received will be summarized by treatment group of the index studies.

Patient incidence rates of AEs will be tabulated by MedDRA system organ class, MedDRA preferred term, and treatment group of the index studies. Narratives of treatment-emergent deaths, serious and significant AEs, including early withdrawals due to AEs, will also be provided.

All treatment-emergent AEs, all treatment-emergent AEs potentially related to Study Drug, all treatment-emergent serious AEs, and all treatment-emergent serious AEs potentially related to Study Drug will be summarized.

Injection Site Reactions (ISRs) will be summarized by treatment group of the index studies, MedDRA preferred term and severity.

Independently adjudicated events of MACE and pancreatitis will be summarized by treatment group of the index studies.

Laboratory tests to ensure patient safety including chemistry panel, complete blood count (CBC) with differential, coagulation panel, IM, complement etc., will be summarized by study visits by treatment group of the index studies.

These safety variables will also be presented as change and percent change from baseline over time after Study Drug administration, as appropriate.

Vital signs, weight, ECG measures, echocardiography assessments, and MRI assessments will be tabulated by treatment group of the index studies.

10.6.3 Efficacy Analysis

Percent change and change from baseline to Month 3, Month 6, and Month 12 in fasting TG will be summarized by treatment group of the index studies. Response rate of patients with fasting plasma TG < 750 mg/dL or achieving fasting TG ≥ 40% reduction from baseline at Month 3, Month 6, and Month 12 will be summarized. Response analysis will also be conducted using a range of fasting plasma TG thresholds for determination of responder status.

Percent change and change from baseline to Month 3, Month 6, and Month 12 will also be summarized by treatment group of the index studies for other fasting lipid measures including non-HDL-C, apoB, HDL-C, apoA-1, VLDL-C, and LDL-C, total cholesterol, and fasting total apoC-III.

The incremental effects of volanesorsen on lipid measures will be explored and the association between changes in lipid parameters and total amount of drug received will be examined, as appropriate.

Frequency and severity of patient reported abdominal pain, adjudicated acute pancreatitis event rate, quality of life assessments, and comparison of other symptoms including eruptive xanthomas and lipemia retinalis will be summarized by treatment group of the index studies.

Additional details of the analyses to be conducted will be provided in the SAP.

10.6.4 Pharmacokinetic and Immunogenicity Analysis

10.6.4.1 Pharmacokinetic Analysis

For all patients, pre-dose and post-treatment volanesorsen plasma concentrations will be summarized using descriptive statistics, with stratification by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16 and IM status.

For patients in the PK subgroup only, non-compartmental PK analysis of volanesorsen will be carried out on each individual patient data set using data collected in the open label extension (OLE) study from the intensive PK subgroup, following a single dose (i.e., single-dose PK) or multiple doses (i.e., steady-state PK), depending on their earlier treatment in the index studies. On Week 1 Day 1 of the OLE study, patients who received placebo in the index study will receive the first treatment of volanesorsen (single-dose PK), while patients who received volanesorsen in the index studies had been on volanesorsen treatment for 12 months (ISIS 304801-CS6) or 6 months (ISIS 304801-CS16), thus the PK data collected from these patients reflect steady-state PK. The maximum observed drug concentration (C_{max}) and the time

taken to reach C_{max} (T_{max}) will be obtained directly from the concentration-time data. Area under the plasma concentration-time curve from time zero to 24 hours ($AUC_{0\text{-}24hr}$) will be calculated using the linear trapezoidal rule. Apparent systemic (plasma) clearance after SC administration ($CL_{0\text{-}24hr}/F_{0\text{-}24hr}$) will be calculated from $CL_{0\text{-}24hr}/F_{0\text{-}24hr}$ = Actual Dose/$AUC_{0\text{-}24hr}$. Mean residence time (MRT) from time zero to 24 hours after the SC administration will be calculated from the equation, $MRT_{0\text{-}24hr} = AUMC_{0\text{-}24hr}/AUC_{0\text{-}24hr}$, where $AUMC_{0\text{-}24hr}$ is the area under the moment plasma concentration-time curve from time zero to 24 hours after the SC administration. Other PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist.

Plasma PK parameters will be summarized using descriptive statistics, with and without stratification by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16 and IM status. Additional details regarding the PK analysis will be described in the SAP.

Population PK, PK/PD, and covariate analysis may be performed if deemed appropriate, and results will be reported separately.

10.6.4.2 Immunogenicity Analysis

Immunogenicity (IM) results (screen positive/negative, confirmed positive/negative or not evaluable, and when applicable, titer of anti-volanesorsen antibodies) before, during, and after treatment with Study Drug (volanesorsen) (i.e., sample [anti-drug antibody] ADA status) will be listed by their prior treatment in study ISIS 304801-CS6 or ISIS 304801-CS16 and study day. Subject ADA status (positive/negative or not evaluable) for all evaluable patients, along with the study day associated with the first positive IM status emerged (T_{first}, i.e., onset of ADA development), the last positive IM status observed (T_{last}), the duration of ADA response (number of days between T_{first} and T_{last}) if appropriate, the last ADA sample collection day, and subject - peak titer if applicable, will be listed by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16 study day. Subjects with positive anti-volanesorsen antibody status may be further classified (when applicable) as being either ‘persistent’, ‘transient’, or ‘not determinable’, if deemed appropriate.

Additionally, the sample and subject IM incidence (number) and incidence rate (percent) will be summarized as the total number and percent of evaluated subjects with antibody negative, positive, and unknown status by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16. Furthermore, onset, duration, and titer of the ADA response, if applicable, will be summarized as median, quartiles (25% and 75%), and range.

Additional details regarding the IM data analysis will be described in the SAP.

Potential relationships between immunogenicity results (e.g., IM status) and selected efficacy (e.g., % change in fasting TG from baseline at 3-, 6-, and 12-month endpoints), safety, and PK (e.g., C_{trough}) measures will be evaluated using graphical analysis and statistical analysis. These analyses will be either conducted and included in the study report, or data pooled and analyzed from all available Phase 2 and 3 studies and reported separately.

11. INVESTIGATOR'S REGULATORY OBLIGATIONS

11.1 Informed Consent

The written informed consent document should be prepared in the language(s) of the potential patient population, based on an English version provided by the Sponsor.

Before a patient's participation in the trial, the Investigator is responsible for obtaining written informed consent from the patient after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific qualification procedures or any Study Drug are administered. The patient must be given sufficient time to consider whether to participate in the study.

The acquisition of informed consent and the patient's agreement or refusal to notify his/her primary care physician should be documented in the patient's medical records and the informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion (not necessarily an Investigator). The original signed informed consent form should be retained in the Study Master File and in any other locations required by institutional policy, and a copy of the signed consent form should be provided to the patient.

11.2 Ethical Conduct of the Study

The Guidelines of the World Medical Association (WMA) Declaration of Helsinki dated October 2002 the applicable regulations and guidelines of current Good Clinical Practice (GCP) as well as the demands of national drug and data protection laws and other applicable regulatory requirements will be strictly followed.

11.3 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent form, other written patient information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by the Sponsor before recruitment of patients into the study and shipment of volanesorsen. A copy of the written approval of any other items/materials that must be approved by the Study Center or IEC/IRB must also be received by the Sponsor before recruitment of patients into the study and shipment of Study Drug. The Investigator's Brochure must be submitted to the IEC/IRB for acknowledgement.

The Investigator must submit to and, where necessary, obtain approval from the IEC/IRB, for all subsequent protocol amendments and changes to the informed consent document. The Investigator should notify the IEC/IRB of deviations from the protocol in accordance with ICH GCP Section 4.5.2. The Investigator should also notify the IEC/IRB of serious adverse events occurring at the Study Center and other adverse event reports received from the Sponsor, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study. Copies of the Investigator's reports, all IEC/IRB submissions and the IEC/IRB continuance of approval must be sent to the Sponsor.

11.4 Patient Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained. On the case report forms (CRF) or other documents submitted to the Sponsor, patients should be identified by unique initials and a patient study number only. Documents that are not for submission to the Sponsor (e.g., signed informed consent forms) should be kept in strict confidence by the Investigator.

In compliance with Federal and local regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the patient to permit named representatives to have access to his/her study-related records without violating the confidentiality of the patient.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments

Protocol amendments must be made only with the prior approval of the Sponsor. Agreement from the Investigator must be obtained for all protocol amendments and amendments to the informed consent document. The regulatory authority and IEC/IRB must be informed of all amendments and give approval for any amendments likely to affect the safety of the patients or the conduct of the trial. The Investigator **must** send a copy of the approval letter from the IEC/IRB to the Sponsor.

12.2 Study Termination

The Sponsor reserves the right to terminate the study according to the terms of the site contract. The Investigator reserves the right to terminate their participation in the study, according to the terms of the site contract. The Investigator/Sponsor should notify the IEC/IRB in writing of the trial's completion or early termination and send a copy of the notification to the Sponsor.

12.3 Study Documentation and Storage

An electronic case report form (eCRF) utilizing an Electronic Data Capture (EDC) application will be used for this study.

The Investigator should ensure that all appropriately qualified persons to whom he/she has delegated trial duties are recorded on a Sponsor-approved Delegation of Site Responsibilities Form.

Source documents are original documents, data, and records from which the patient's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, imaging, and correspondence. In this study, CRFs may not be used as source documents.

The Investigator and Study Center staffs are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation in accordance with

Section 8 of the ICH Guidelines (E6), suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Elements should include:

- Patient files containing completed CRFs, informed consents, and supporting copies of source documentation
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation and all correspondence to and from the IEC/IRB and the Sponsor
- If volanesorsen supplies are maintained at the Study Center, proof of receipt, volanesorsen Accountability Record, Return of volanesorsen for Destruction, final study volanesorsen reconciliation, and all volanesorsen-related correspondence

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

No study document should be destroyed without prior written agreement between the Sponsor or and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor.

12.4 Study Monitoring

The Sponsor representative and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the trial (e.g., CRFs and other pertinent data) provided that patient confidentiality is respected.

The Sponsor monitor is responsible for inspecting the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to patient medical records and other study-related records needed to verify the entries on the CRFs.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's Clinical Quality Assurance Department. Inspection of Study Center facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the trial conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

To ensure the quality of clinical data a clinical data management review will be performed on patient data received by the Sponsor. During this review, patient data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or Study Center notifications will be sent to the Study Center for completion and return to Sponsor.

The Principal Investigator will sign and date the indicated places on the CRF. These signatures will indicate that the principal Investigator inspected or reviewed the data on the CRF, the data queries, and the Study Center notifications, and agrees with the content.

12.5 Language

Case report forms must be completed in English. Generic names for concomitant medications should be recorded in English if possible, unless it is a combination drug, then record the trade name in English.

All written information and other material to be used by patients and investigative staff must use vocabulary and language that are clearly understood.

12.6 Compensation for Injury

The Sponsor maintains appropriate insurance coverage for clinical trials and will follow applicable local compensation laws. Patients will be treated and/or compensated for any study-related illness/injury in accordance with the information provided in the Compensation for Injury section of the Informed Consent document.

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14. APPENDICES

Appendix A Schedule of Procedures

Appendix A Schedule of Procedures

Study Period		Qual[a]	Treatment Period																					Post Treatment Follow-up	
Study Week		-2 to -1	Wk 1		Wk 4	Wk 8	Month 3		Wk 16	Wk 19	Wk 22	Month 6		Wk 29	Wk 32	Wk 35	Wk 38	Wk 41	Wk 44	Wk 47	Month 12		Wk 58	Wk 65
							Wk 12	Wk 13				Wk 25	Wk 26								Wk 51	Wk 52 or ET		
Study Day		-14 to -7	1	2	22	50	78	85	106	127	148	169	176	197	218	239	260	281	302	323	351	358	400	449
Visit Window+/- Days		0	0	0	2	2	2	2	3	3	3	2	2	3	3	3	3	3	3	3	2	2	7	7
Informed Consent		X																						
Outpatient Visit		X	X	X[k]	X[k]	X[k]	X[k]	X	X[k]	X[k]	X[k]	X[k]	X	X[k]	X[k]	X[k]	X	X[k]	X[k]	X[k]	X[k]	X	X[k]	X
Inclusion/Exclusion Criteria		X																						
Vital Signs + body weight (+ height on Day 1 only)		X	X		X	X		X					X				X					X		X
Physical Examination			X					X					X				X					X		X
12- lead ECG (triplicate)								X					X				X					X		X
MRI (liver/spleen)																						X[l]		
Echocardiography													X[l]									X[l]		
Blood Draw (Fasting)[c]	Chemistry Panel	X	X		X	X		X		X			X		X		X		X			X	X	X
	CBC with Differential[b]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Serum Lipid Panel	X	X		X	X	X	X				X	X				X				X	X		X
	Coagulation (aPTT, PT, INR)	PG				X		X					X				X					X		
	hsCRP, HbA1c, FPG, and de-lipidated free glycerol		X					X					X									X		X
	Sedimentation Rate		X					X					X									X		X
	Complement (C5a, Bb)		X					X					X									X		X
	Plasma PK - Volanesorsen		X[m]	X	X	X		X					X				X					X		X
	Anti-Volanesorsen Antibodies		X		X	X		X					X				X					X		X
	FSH (women only, if applicable)																							
	Serum Pregnancy Test[d]	X			X	X		X		X			X		X		X		X			X	X	X
	Archived Serum & Plasma Samples[e]		X			X		X					X									X		X

Appendix A Schedule of Procedures *Continued*

Study Period	Qual[a]	Treatment Period																				Post Treatment Follow-up	
Study Week	-2 to -1	Wk 1		Wk 4	Wk 8	Month 3		Wk 16	Wk 19	Wk 22	Month 6		Wk 29	Wk 32	Wk 35	Wk 38	Wk 41	Wk 44	Wk 47	Month 12		Wk 58	Wk 65
						Wk 12	Wk 13				Wk 25	Wk 26								Wk 51	Wk 52 or ET		
Study Day	-14 to -7	1	2	22	50	78	85	106	127	148	169	176	197	218	239	260	281	302	323	351	358	400	449
Visit Window+/- Days	0	0	0	2	2	2	2	3	3	3	2	2	3	3	3	3	3	3	3	2	2	7	7
Urinalysis[c]	X	X[n]		X	X		X[n]		X[n]			X[n]		X[n]		X[n]		X[n]			X[n]	X[n]	X[n]
Fundus Photography[f]	X																				X[l]		
Genetic testing for FCS diagnosis (if not available in medical history)[g]	X																						
Postheparin Lipoprotein Lipase activity[h]	X																						
Weekly Study Drug: SC Injection		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Symptom Diary (weekly)	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Assessment(s)		X					X					X									X		X
Food/Drink Diary (quarterly)[i]		X					X					X									X		X
Diet/Alcohol Counseling[j]	X	X		X	X		X					X				X					X	X	X
Adverse Events	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a Qualification procedures performed (Please refer to Section 4.1)

b Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are unreportable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1-week and determined not to have met a stopping rule before dosing can continue. Any case of a platelet count ≤ 50,000/mm^3 should be reported in an expedited fashion to the Sponsor

c Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours. During treatment period urine and blood samples will be collected prior to Study Drug administration. Does not apply to 24-hour PK blood draw

d Females of childbearing potential only

e Serum and plasma samples will be collected and stored for follow-up exploration of laboratory findings and/or adverse events (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.) in this or subsequent clinical studies of volanesorsen

Appendix A Schedule of Procedures Continued

Legend Text *Continued*

f If possible, fundus photography should be completed prior to administration of the first dose of Study Drug (ISIS 304801-CS16 rollover patients) and repeated at Week 52 (Please refer to Section 6.2.2.2)

g Genetic testing can be conducted for study qualification (ISIS 304801-CS16 rollover patients); genetic testing will only be conducted if allowed in the geographic region and only after the patient has given specific written informed consent for genetic testing

h Post-heparin lipoprotein lipase activity can be conducted for study qualification (ISIS 304801-CS16 rollover patients; please refer to Section 6.2.10)

i In addition to diary, patients will be contacted at random times during the study to review their current eating and drinking habits

j To reinforce compliance to the diet and alcohol restrictions. Random diet/alcohol assessments (phone visits) will also be performed by dietician or study personnel

k Assessments and procedures to be conducted by either a home healthcare nurse, or the Study Center as arranged by the Study Center personnel

l A ± 7-day window is allowed for MRI, echocardiography procedures and fundus photography

m Full or abbreviated PK profile (see Appendix C)

n Expanded urinalysis (see Appendix B)

Appendix B List of Laboratory Analytes

Appendix B List of Laboratory Analytes

Based on emerging data from this or future studies, additional tests not listed below may be performed on stored samples to better characterize the profile of volanesorsen or other similar oligonucleotides.

Clinical Chemistry Panel

- Sodium
- Potassium
- Chloride
- Bicarbonate
- Total protein
- Albumin
- Calcium
- Magnesium
- Phosphorus
- Glucose
- BUN
- Creatinine
- Uric Acid
- Total bilirubin
- Direct (conjugated) bilirubin
- Indirect (unconjugated) bilirubin
- ALT
- AST
- Alkaline phosphatase

Coagulation

- aPTT (sec)
- PT (sec)
- INR

Lipid Panel

- Total Cholesterol
- LDL-C
- HDL-C
- Triglycerides
- Non-HDL-C
- VLDL-C
- apoA-1
- apoB
- apoC-III

Hematology

- Red blood cells
- Hemoglobin
- Hematocrit
- MCV, MCH, MCHC
- Platelets
- White blood cells
- WBC Differential (% and absolute)
  - Neutrophils
  - Eosinophils
  - Basophils
  - Lymphocytes
  - Monocytes

Pharmacokinetics[1] & Immunogenicity

- Volanesorsen levels in plasma
- Anti-volanesorsen antibodies in plasma

Other Assessments

- hsCRP
- Sedimentation Rate
- C5a, Bb
- De-lipidated free glycerol
- HbA1c, FPG

Urinalysis

- Color
- Appearance
- Specific gravity
- pH
- Protein
- Blood
- Ketones
- Urobilinogen
- Glucose
- Bilirubin
- Leukocyte esterase
- Nitrate
- Microscopic examination[2]

Additional Measures for Expanded Urinalysis

- Total protein (quantitative)
- Microalbumin
- β2-microglobulin

1 Plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, IM testing (or possibly for purposes of IM assay development and/or validation), or to assess other actions of volanesorsen with plasma constituents

2 Will be performed on abnormal findings unless otherwise specified

Appendix C Pharmacokinetic Sampling Schedule

Appendix C Pharmacokinetic Sampling Schedule

Blood samples for the determination of plasma volanesorsen concentrations will be collected prior to dosing, and at various times throughout the dosing and post-treatment follow-up period as noted in the tables below.

PK Sampling Schedule (All Patients except PK Subgroup)

Week	Wk 1	Wk 4	Wk 8	Wk 13	Wk 26	Wk 38	Wk 52	Wk 65
Study Day	**D1**	**D22**	**D50**	**D85**	**D176**	**D260**	**D358**	**D449**
Visit Window +/- Days	0	2	2	2	2	3	2	7
Time Point	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime

PK Sampling Schedule (PK Subgroup only*)

Week	Wk 1	Wk 1	Wk 4	Wk 8	Wk 13	Wk 26	Wk 38	Wk 52	Wk 65
Study Day	**D1**	**D2**	**D22**	**D50**	**D85**	**D176**	**D260**	**D358**	**D449**
Visit Window +/- Days	0	0	2	2	2	2	3	2	7
Time Point	Pre-dose, 1, 2, 3, 4, 6, 8, and 12 hrs post-dose	24 hrs post-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime

* Patients at selected sites will be asked to participate in the extended 24-hour PK profile beginning on Study Day 1. Participation is optional

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

The following grading recommendations for adverse events relating to lab test abnormalities are based upon the **Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010**

Adverse Event	Mild	Moderate	Severe
Hematology			
aPTT prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage
Eosinophils increased†	650 – 1,500 cell/mm^3	1,501 - 5,000 cell/mm^3	>5,000 cell/mm^3
Fibrinogen decreased	<1.0 - 0.75 x LLN or <25% decrease from baseline	<0.75 - 0.5 x LLN or 25 - <50% decrease from baseline	<0.5 x LLN or ≥50% decrease from baseline
Hemoglobin decreased (Anemia)	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated
Hemoglobin increased	Increase in >0 - 2 g/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 g/dL above ULN or above baseline if baseline is above ULN	Increase in >4 g/dL above ULN or above baseline if baseline is above ULN
INR increased	>1 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation
Lymphocyte count decreased	<LLN - 800/mm^3; <LLN - 0.8 x 10^9/L	<800 - 500/mm^3; <0.8 - 0.5 x 10^9 /L	<500 /mm^3; <0.5 x 10^9 /L
Lymphocyte count increased	-	>4000/mm^3 - 20,000/mm^3	>20,000/mm^3
Neutrophil count decreased	<LLN - 1500/mm^3; <LLN - 1.5 x 10^9 /L	<1500 - 1000/mm^3; <1.5 - 1.0 x 10^9 /L	<1000/mm^3; <1.0 x 10^9 /L
Platelet count decreased	<LLN - 75,000/mm^3; <LLN - 75.0 x 10^9 /L	<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9 /L	<50,000/mm^3; <50.0 x 10^9 /L
White blood cell decreased	<LLN - 3000/mm^3; <LLN - 3.0 x 10^9 /L	<3000 - 2000/mm^3; <3.0 - 2.0 x 10^9 /L	<2000/mm^3; <2.0 x 10^9 /L
Chemistry			
Acidosis	pH <normal, but >=7.3	-	pH <7.3
Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Alkalosis	pH >normal, but ≤7.5	-	pH >7.5
Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 x ULN
Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

Adverse Event	Mild	Moderate	Severe
Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer
CD4 lymphocytes decreased	<LLN - 500/mm^3; <LLN - 0.5 x 10^9 /L	<500 - 200/mm^3; <0.5 - 0.2 x 10^9 /L	<200/mm^3; <0.2 x 10^9 /L
CPK increased*	>ULN - <6 ULN	6 - 10 x ULN	>10 x ULN
Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 x ULN
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 mg/dL; >3.1 mmol/L; Ionized calcium >1.6 mmol/L; hospitalization indicated
Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 mg/dL; >13.9 mmol/L; hospitalization indicated
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0; hospitalization indicated
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 mg/dL; >1.23 mmol/L
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 mmol/L; hospitalization indicated
Hyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 mg/dL; <1.75 mmol/L; Ionized calcium <0.9 mmol/L; hospitalization indicated
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 mg/dL; <3.0 mmol/L	<40 mg/dL (<2.2 mmol/L) AND requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions‡
Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 mmol/L; hospitalization indicated
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 mg/dL; <0.4 mmol/L
Hyponatremia	<LLN - 130 mmol/L	-	<130 mmol/L
Hypophosphatemia	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 mg/dL; <0.6 mmol/L
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

Adverse Event	Mild	Moderate	Severe
Urine			
Proteinuria Adults Children	1+ proteinuria; urinary protein <1.0 g/24 hrs -	2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs; Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Urinary protein ≥3.5 g/24 hrs; Urine P/C >1.9
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated

[†]Grading for this parameter is derived from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007

*Grading for this parameter is derived from the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0, Nov 2014

[‡]Modified for consistency with the ADA and Endocrine Society Guidelines (Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. Diabetes Care 2013;36:1384-95)

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ISIS 304801-CS7

The APPROACH Open Label Extension Study

Volanesorsen (ISIS 304801)

An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol Amendment 2 –22 April 2016

EudraCT No: 2015-003755-21

ISIS 304801-CS7

The APPROACH Open Label Extension Study

Volanesorsen (ISIS 304801)

An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol Amendment 2 – 22 April 2016

Protocol History:

Original Protocol:	28 August 2015
Protocol Amendment 1:	2 February 2016

Sponsor:

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Ionis Protocol Number: ISIS 304801-CS7

Protocol Amendment 2

EudraCT No: 2015-003755-21

Clinical Phase: 3

The APPROACH Open Label Extension Study

Volanesorsen (ISIS 304801)

An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

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Date: 22 April 2016

Confidentiality Statement

This document contains confidential information of Ionis Pharmaceuticals, Inc., that must not be disclosed to anyone other than the recipient study staff and members of the independent ethics committee, institutional review board, or authorized regulatory agencies. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc.

Protocol Signature Page

Protocol Number: ISIS 304801-CS7

Protocol Title: An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Amendment: Amendment 2

Date: 22 April 2016

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)", dated 22 April 2016, and agree to conduct the study as described herein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice (E6).

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc.

_____

Investigator's Signature

_____ _____

Investigator's Name *(please print)* Date (DD Month YYYY)

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PROTOCOL AMENDMENT

Protocol Number:	ISIS 304801-CS7
Protocol Title:	An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Amendment Number:	2
Amendment Date:	22 April 2016

The purpose of this protocol amendment is to implement the following modifications to Protocol ISIS 304801-CS7 Amendment 1 dated 02 February 2016:

1. To modify the clinical experience safety language to reflect updated blinded safety data from ongoing studies.
2. To indicate that the DSMB is independent.
3. To revise the contraceptive requirements to state that abstinence is only acceptable as true abstinence, i.e., when it is in line with the preferred and usual lifestyle of the patient.
4. To add lipoprotein lipase activity as a qualification assessment for ISIS 304801-CS16 rollover patients.
5. To add genetic testing as a qualification assessment for ISIS 304801-CS16 rollover patients.
6. To increase the frequency of the pregnancy testing.
7. To add hematology blood draws at Weeks 12, 16, 22, 25, 29, 35, 41, 47, and 51 to more frequently assess platelet counts.
8. To allow blood sampling at Weeks 4, 8, 12, 16, 19, 22, 25, 29, 32, 35, 41, 44, 47, 51, and 58 to be conducted by a home healthcare nurse.
9. To allow blood sampling at the 24-hour PK blood draw to be conducted by a home healthcare nurse.
10. To add language that each time a hematology lab is drawn and sent to the central laboratory for analysis, an additional sample should be collected in parallel and analyzed locally, to reduce the occurrence of unreportable hematology results.
11. To provide guidance that the length of fasting should preferably not be more than 12 hours.

12. To update platelet monitoring rule language to allow for more frequent monitoring as determined by the Sponsor Medical Monitor in consultation with the Investigator.

13. To add language to the safety monitoring for insulin, oral antidiabetic medication and glucose that all patients, including those not on insulin, who use a glucometer should also bring their glucometer and/or glucometer log printout to every clinic visit.

14. To clarify guidance on determining relatedness of a SUSAR.

Minor administrative changes or corrections (not included in the list of changes) have been made throughout the protocol in order to improve the overall clarity of the protocol but these changes do not impact the study design.

The following table provides a summary list of changes to the protocol:

Protocol Section	Description of Change	Rationale
Section 2.3.4 Clinical Experience	In the completed studies there have been no ISIS 304801 associated laboratory abnormalities suggestive of an effect on the renal (serum creatinine, proteinuria) or hepatic systems (alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin). In Phase 2 studies, there was a mild decrease of platelet count associated with ISIS 304801 administration that recovered in the post-treatment period and was not associated with platelet-related adverse events. In the blinded ongoing clinical trials of ISIS 304801, 2 patients of 142 dosed (as of February 29, 2016) had a decrease in platelet count to less than 50,000/mm^3 in the absence of major bleeding or clinically-relevant non-major bleeding and had Study Drug paused as per the monitoring and stopping rules for platelet counts (Section 8.6.3). Platelet counts recovered following suspension of dosing.	To modify the clinical experience safety language to reflect updated blinded safety data from ongoing studies
Section 3.6 Data and Safety Monitoring Board	Independent added before Data and Safety Monitoring Board (DSMB)	To clarify that the DSMB is independent
Protocol Synopsis Study Population Section 5.1 Inclusion Criteria Section 6.3.1 Contraception Requirements	Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception	Per the MHRA's guidance to state that only true abstinence would be acceptable, and that periodic abstinence is not an acceptable method of contraception
Section 6.2.10 Lipoprotein Lipase Activity Sample Collection Appendix A Schedule of Procedures	Lipoprotein lipase (LPL) activity will be measured in ISIS 304801-CS16 rollover patients if needed for study qualification. In brief, fasted patients will be given a low intravenous dose of heparin. A blood sample will be drawn prior to and at 10 or 15 minutes after the heparin administration for measurement of LPL activity as per instructions provided to the Investigator. Post heparin lipoprotein lipase activity can be conducted for study qualification (ISIS 304801-CS16 rollover patients; please refer to Section 6.2.10)	Lipoprotein lipase activity added as a qualification assessment for ISIS 304801-CS16 rollover patients

Protocol Section	Description of Change	Rationale
Appendix A Schedule of Procedures	Genetic testing can be conducted for study qualification (ISIS 304801-CS16 rollover patients); genetic testing will only be conducted if allowed in the geographic region and only after the patient has given specific written informed consent for genetic testing	Genetic testing added as a qualification assessment for ISIS 304801-CS16 rollover patients
Appendix A Schedule of Procedures	Pregnancy testing was added at Weeks 4, 19, 32, 44, and 58	To reduce the time period between pregnancy tests
Appendix A Schedule of Procedures	Hematology blood draws were added at Weeks 12, 16, 22, 25, 29, 35, 41, 47, and 51	To implement more frequent evaluation of platelet counts to assess platelet fluctuations during the course of the study and to increase monitoring of platelet counts in patients for safety purposes
Section 6.1.2 Treatment Period Appendix A Schedule of Procedures	Blood sampling at Weeks 4, 8, 12, 16, 19, 22, 25, 29, 32, 35, 41, 44, 47, 51, and 58 may be conducted by a home healthcare nurse	To decrease study burden on the patient by removing the requirement for a visit to the clinic or study center for blood draws
Section 6.1.3 Pharmacokinetic (PK) Subgroup Appendix A Schedule of Procedures	Patients in this subgroup will have an additional visit to the clinic, or by a home healthcare nurse, on Day 2 to collect a 24-hour post-dose blood draw after dosing on Day 1	To decrease study burden on the patient by removing the requirement for a visit to the clinic or study center for the 24-hour PK blood draw
Appendix A Schedule of Procedures	Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are uninterpretable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1-week.	To reduce the occurrence of unreportable hematology results (e.g., hemolyzed or clumped blood samples)
Section 6.3.2 Treatment Period Appendix A Schedule of Procedures	Wording was added to note that fasting should preferably not be more than 12 hours	To provide guidance on the length of fasting
Section 8.5.2 Safety Monitoring for Platelet Count Results	Addition to platelet monitoring rules that more frequent testing may also be required	To allow more frequent monitoring of platelets when appropriate
Section 8.5.6 Safety Monitoring for Insulin, Oral Antidiabetic Medication and Glucose	In addition, patients who are not on insulin (e.g., patients with type 2 diabetes), but use a glucometer should also bring their glucometer and/or glucometer log printout to every clinic visit.	To implement that all patients, including those not on insulin, who use a glucometer should also bring their glucometer and/or glucometer log printout to every clinic visit
Section 9.2 Regulatory Requirements	In addition to the Investigator's assessment of relatedness, the Sponsor or designee will evaluate the available information and perform an independent assessment of relatedness. While the Sponsor may upgrade an Investigator's decision it is not permissible to downgrade the Investigator's opinion for the purposes of determining whether the SAE meets the definition of a SUSAR.	To clarify guidance on determining relatedness of a SUSAR

PROTOCOL SYNOPSIS

Protocol Title	An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Study Phase	3
Indication	Familial Chylomicronemia Syndrome
Study Objectives	To evaluate the safety and efficacy of extended dosing with volanesorsen (volanesorsen sodium 300 mg) in patients with FCS
Study Design	This is a multi-center, open-label extension study of ISIS 304801-CS6 and ISIS 304801-CS16. All patients will receive volanesorsen 300 mg once per week for 52 weeks. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period. Following the Week 52 visit, patients will enter a 13-week post-treatment evaluation period.
Number of Patients	Up to approximately 70 patients dosed
Study Population	Inclusion Criteria: 1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law 2. Age ≥ 18 years at time of informed consent 3. Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement. Patients who are enrolled in ISIS 304801-CS16 must also meet the following criteria in order to enter into the Extension Study: a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L) b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) by documentation of at least 1 of the following: • Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1) • Post heparin plasma LPL activity of ≤ 20% of normal c. Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 study 4. Able and willing to participate in a 65-week study 5. Satisfy 1 of the following: a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved), abstinent*, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration

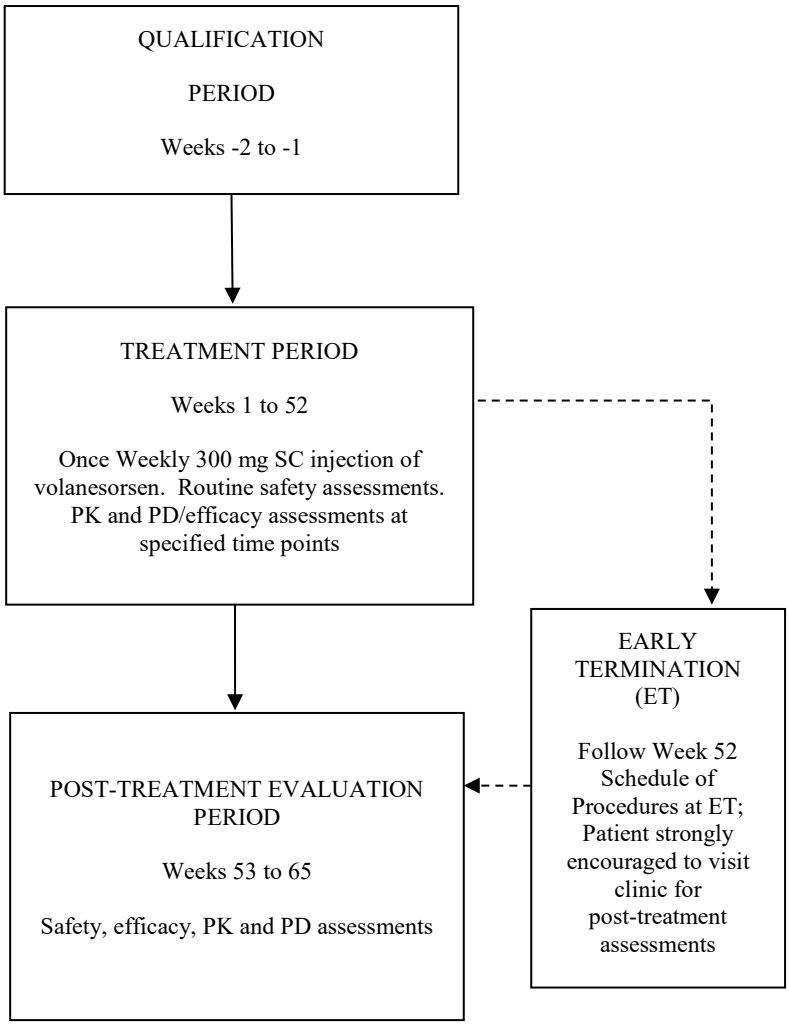
PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	Inclusion Criteria: *Continued* b. Males: Surgically sterile, abstinent* or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration * Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception Exclusion Criteria: 1. Have any new condition or worsening of existing condition which in the opinion of the Investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study 2. Unwilling to comply with lifestyle requirements for the duration of the study (Section 6.3)
Treatment Group	Volanesorsen 300 mg once per week
Study Drug Administration	Volanesorsen will be administered as subcutaneous (SC) injections.
Dose Adjustments	Dose adjustments, including dose interruptions and/or decreasing the dose frequency will be allowed for safety or tolerability after consultation with the Sponsor Medical Monitor.
Rationale for Dose and Schedule Selection	The dose of 300 mg once weekly was chosen for the double-blinded placebo-controlled Phase 3 index studies (ISIS 304801-CS6- and ISIS 304801-CS16) based on the pharmacodynamic and safety analysis of the Phase 2 studies which included a subset of patients with FCS. This is an extension to the ISIS 304801-CS6 and ISIS 304801-CS16 index studies. Only the subset of patients from ISIS 304801-CS16 with FCS diagnosis may enter the Extension Study. (Please refer to inclusion criteria #3, above)
Study Visit Schedule and Procedures	The study for an individual patient will generally consist of the following periods: • A qualification period of up to 2 weeks (unless approved by the Sponsor). Please refer to Section 4.1 and Appendix A. A 52-week treatment period during which volanesorsen will be administered as a once weekly SC injection • A 13-week post-treatment evaluation period The patients, Investigators, study staff, and the Sponsor will remain blinded to lipid data through the last patient's Week 13 visit of the extension study or until results from the database locks for the ISIS 304801-CS6 and ISIS 304801-CS16 index studies becomes available, whichever comes first. Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), adverse events (AE), concomitant medication/procedure information, lipid panel, volanesorsen plasma concentrations, immunogenicity (IM) testing, liver/spleen magnetic resonance imaging (MRI), ECGs, echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Dietary counseling will be repeated at intervals throughout the treatment and follow-up period and a daily food/drink diary will be completed for the week prior to each quarterly visit by each patient. Following the Week 52 visit, patients will enter the 13-week post-treatment evaluation period.

PROTOCOL SYNOPSIS *Continued*

Safety and Tolerability Evaluations	Overall safety and tolerability of volanesorsen will be assessed by determining the incidence and severity of adverse and serious adverse events (including independently adjudicated events of acute pancreatitis and MACE), withdrawals due to adverse events, and changes in laboratory and other safety parameters.
Planned Analyses	Safety Endpoints: • Adverse events including adjudicated events of acute pancreatitis and MACE • Vital signs and weight • Physical examinations • Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis) • Echocardiography • Electrocardiograms (ECGs) • Use of concomitant medications • MRIs Efficacy Endpoints: • Percent change and absolute change from baseline in fasting TG • Frequency and severity of patient reported abdominal pain during the treatment period • Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-high-density lipoprotein-cholesterol (non-HDL-C), apolipoprotein B [apoB], high-density lipoprotein-cholesterol (HDL-C), apolipoprotein A-1 [apoA-1], very-low-density lipoprotein-cholesterol (VLDL-C), and LDL-C • Percent change from baseline in fasting total apolipoprotein C-III (apoC-III) • Quality of Life questionnaires (EQ-5D, SF-36) • Adjudicated acute pancreatitis event rate • Other symptoms: eruptive xanthoma, lipemia retinalis
Pharmacokinetic Evaluations	Plasma samples will be taken from all patients for the measurement of volanesorsen as follows: trough levels (pre-dose) throughout treatment and post-treatment levels during the post-treatment follow-up period. In a subset of patients, more frequent assessment of plasma concentrations of volanesorsen will be performed to determine volanesorsen pharmacokinetic parameters. Plasma sample collection time points are detailed in Appendix A and Appendix C.
Statistical Considerations	No sample size calculations were performed as this is an extension study to the double-blind placebo controlled ISIS 304801-CS6 and ISIS 304801-CS16 index studies.
Sponsor	Ionis Pharmaceuticals, Inc.
Collaborator	Akcea Therapeutics

STUDY DESIGN AND TREATMENT SCHEMA



STUDY GLOSSARY

Abbreviation/Acronym	Definition
ADA	anti-drug antibody
AE	adverse Event
ALP	alkaline Phosphatase
ALT	alanine Aminotransferase
ANA	antinuclear Antibody
apoA-1	apolipoprotein A-1
apoB	apolipoprotein B
apoC-III	apolipoprotein C-III
apoE	apolipoprotein E
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
CBC	complete blood count
C_{max}	maximum observed drug concentration
CRF	case report form
DNA	deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
ET	early termination
FAS	full analysis set
FCS	Familial Chylomicronemia Syndrome
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
GPIHBP1	Glycosylphosphatidylinositol-anchored HDL-binding Protein 1
HAPI	Heritability and Phenotype Intervention
HbA1c	Glycated Hemoglobin
HDL	High-Density Lipoprotein
HDL-C	High-Density Lipoprotein-Cholesterol
hsCRP	High-sensitivity C-reactive protein
ICH	International Conference on Harmonization
IDL	Intermediate density lipoprotein
IEC	Independent Ethics Committee
IM	immunogenicity
Index Studies	ISIS 304801-CS6 and ISIS 304801-CS16

INR	International Normalized Ratio
IRB	Institutional Review Board
IXRS	Interactive Voice/Web-Response System
LDL	Low-Density Lipoprotein
LDL-C	Low-Density Lipoprotein-Cholesterol
LMF1	Lipase Maturation Factor 1
LPL	Lipoprotein Lipase
MACE	Major Acute Cardiovascular Event
MOE	2′-*O*-(2-methoxyethyl)
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NCS	not clinically-significant
NOAEL	No-Observed-Adverse-Effect Level
non-HDL-C	Non-High-Density Lipoprotein-Cholesterol
OLE	Open Label Extension
OTC	over the counter
PFS	prefilled syringe
PD	pharmacodynamic
PK	pharmacokinetic
PPS	per protocol set
PT	prothrombin time
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SUSAR	suspected unexpected serious adverse reaction
T2DM	type 2 diabetes mellitus
T_{max}	time to maximal concentration
TG	triglycerides
Treatment-emergent	occurring after first dose of Study Drug
TRL	Triglyceride-Rich Lipoproteins
ULN	upper limit of normal
VLDL	Very-Low-Density Lipoprotein
VLDL-C	Very-Low-Density Lipoprotein-Cholesterol
VLDL-TG	Lipoprotein-Triglyceride
WMA	World Medical Association

1. OBJECTIVES

The objective of the study is to evaluate the safety and efficacy of extended dosing with volanesorsen in patients with familial chylomicronemia syndrome.

2. BACKGROUND AND RATIONALE

2.1 Overview of Disease

Familial Chylomicronemia Syndrome (FCS) is an inherited disease characterized by severe hypertriglyceridemia and chylomicronemia, and risk or history of pancreatitis. It is a rare autosomal recessive disease that can be diagnosed either in childhood or adulthood.

Fasting plasma triglyceride (TG) levels in FCS patients are typically 10-fold to 100-fold above normal (1,500 to 15,000 mg/dL), despite extreme dietary fat restriction (20 g or approximately 15-20% of daily calorie intake) (Brunzell 1999-2011). Patients with FCS often present in infancy or childhood with frequent and severe abdominal pain, repetitive colicky pain, repeated episodes of potentially fatal acute pancreatitis, and failure to thrive (Brunzell 1999-2011; Tremblay et al. 2011). Physical examination frequently reveals eruptive xanthomas, lipemia retinalis and hepatosplenomegaly, and plasma from patients appears lactescent, interfering with determination of other laboratory parameters (Tremblay et al. 2011).

Patients with fasting triglyceride levels > 10 mmol/L probably have a component of chylomicronemia. Clinical diagnosis would include evidence of clinical features of chylomicronemia syndrome and secondary causes such as uncontrolled type 1 or type 2 diabetes mellitus (T2DM), hypothyroidism, poor diet, alcohol use, nephrotic syndrome or use of associated medications should be ruled out. The diagnosis of FCS may be made more specifically by genotyping or confirmation of very low or absent lipoprotein lipase (LPL) enzyme activity in post heparin plasma (Brunzell 1999-2011).

Patients with FCS carry a heavy burden of medical complications, the most serious, as described above, being an extreme risk of recurrent and potentially fatal pancreatitis. Due to the recurrent episodes of acute pancreatitis, these patients may also develop chronic pancreatitis and signs of exocrine or endocrine pancreatic insufficiency, including diabetes mellitus (Gaudet et al. 2013). While the pathophysiology underlying chylomicron-related pancreatitis has not been completely elucidated, 1 hypothesis is that large chylomicrons lodged in pancreatic capillaries are exposed to pancreatic lipase, with the subsequent release of free fatty acids through the hydrolysis of chylomicron-associated TGs. High concentrations of free fatty acids are thought to damage pancreatic cells leading to emergent pancreatitis (Yang et al. 2009; Berglund et al. 2012).

The etiology of extreme hypertriglyceridemia in FCS is considered to be ineffective triglyceride clearance, due to an extremely low level of LPL activity. LPL normally functions to hydrolyze triglycerides (TG) in chylomicrons along the luminal surface of capillaries, mainly in heart, skeletal muscle, and adipose tissue, promoting triglyceride clearance from the circulation. LPL is regulated by a number of key genes, and loss-of-function mutations in one of these genes, or the LPL gene itself, results in FCS (Surendran et al. 2012). In addition to loss of function mutations, null mutations, and nonsense mutations in the LPL gene, other genes currently identified in FCS patients, and known to directly influence LPL activity include: apolipoprotein C-II (APOC2) a cofactor for LPL (Schuster et al. 2011); apolipoprotein A-V

(APOA5) an enhancer of LPL activity (Schaap et al. 2004); lipase maturation Factor 1 (LMF1), a transmembrane protein involved in LPL maturation (Doolittle et al. 2009); glycosylphosphatidylinositol-anchored HDL-binding protein 1 (GPIHBP1), a capillary endothelial cell protein that provides a platform for LPL-mediated processing of chylomicrons (Beigneux et al. 2007).

2.2 Therapeutic Rationale

Apolipoprotein C-III (ApoC-III), a key regulator of plasma triglyceride levels, is a 79 amino acid glycoprotein synthesized principally in the liver (Ooi et al. 2008; Figure 1). ApoC-III is a major regulator of lipoprotein metabolism and plays a pivotal role in regulating plasma TG levels (Chan et al. 2008). It is a component of triglyceride-rich lipoproteins (TRLs) and a potent inhibitor of LPL (Lemieux et al. 2003). At higher concentrations apoC-III also inhibits hepatic lipase activity (Kinnunen and Ehnolm 1976), an enzyme which plays an important role in the conversion of dense very-low-density lipoprotein (VLDL) to intermediate density lipoprotein (IDL) and to LDL (Mendivil et al. 2010), as well as in the remodeling of HDL (Brown et al. 2010). In addition, increased apoC-III content adversely affects apoE-mediated hepatic uptake of TG-rich remnants (Mann et al. 1997). Thus, elevated plasma apoC-III levels are associated with impaired hydrolysis and retarded clearance of TG-rich particles, resulting in the accumulation of lipoprotein-triglyceride (VLDL-TG) and chylomicrons in plasma and the development of hypertriglyceridemia (Ito et al. 1990).

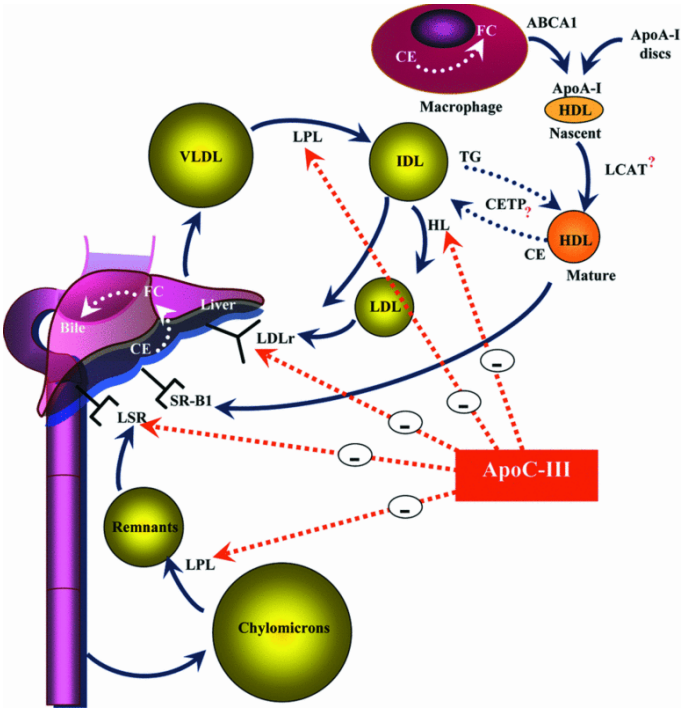


Figure 1 ApoC-III Regulates Lipoprotein Metabolism by Multiple Mechanisms

From Ooi et al. 2008; ABCA1 = ATP-binding cassette A1, apo = apolipoprotein, CE = cholesterol ester, CETP = cholesterol ester transfer protein, FC = free cholesterol, HDL = high-density lipoprotein, HL = hepatic lipase, IDL = intermediate-density lipoprotein, LCAT = lecithin cholesterol acyltransferase, LDL = low-density lipoprotein, LDLr = LDL receptor, LPL = lipoprotein lipase, LSR = lipolysis-stimulated receptor, SR-B1 = scavenger receptor B-1, TG = triglyceride, VLDL = very low-density lipoprotein.

Mechanistically, FCS is primarily a consequence of ineffective clearance of TRL. ApoC-III is a prominent component of TRL (e.g., VLDL and chylomicrons). In addition to its role in inhibiting LPL, apoC-III inhibits TRL remnant (TG-depleted remnant lipoprotein) uptake by hepatic lipoprotein receptors by steric inhibition of the interaction of apoE with these receptors.

Human genetic data have demonstrated positive phenotypic associations with loss (e.g., null or nonsense mutations) and negative effects with gain of function mutations (Atzmon et al. 2006; Pollin et al. 2008; Petersen et al. 2010). A novel nonsense mutation in the apoC-III gene was identified in the heritability and phenotype intervention (HAPI) heart study in Old Order Amish that results in lower plasma apoC-III and TG levels and lower LDL-C, increased HDL-C and reduced atherosclerosis (Pollin et al. 2008). In another study involving a group of 214 Ashkenazi Jews of advanced age (had passed or nearly reached 100 years of age), genotype analysis revealed a polymorphism in the apoC-III gene (APOC3-641CC genotype) with a clear pattern of age-dependent frequency that was associated with significantly lower levels of apoC-III protein, a favorable lipoprotein profile and increased longevity (Atzmon et al. 2006). In contrast to the Amish and Ashkenazi apoC-III polymorphisms associated with lower plasma TG, apoC-III polymorphisms associated with higher plasma TG have also been recently described (Petersen et al. 2010). In a cohort of lean (mean body mass index [BMI] = 24.7 ± 3.6 kg/m^2) Asian Indians, carriers of apoC-III variant alleles (C-482T, T-455C, or both) were noted to have significantly higher plasma apoC-III and TG levels, and decreased ability to clear postprandial plasma TG from the circulation. Taken together, the available data strongly support the development of a therapy that reduces plasma apoC-III levels in order to reduce the very high circulating triglyceride and chylomicron levels that are accompanied by increasing risk for acute pancreatitis.

Given the profound reductions in TGs observed with volanesorsen treatment in FCS patients who have no detectable LPL activity (See Section 2.3.4), and the mechanistic data available to date on apoC-III function, potential mechanisms that explain how apoC-III inhibition results in triglyceride reduction in FCS patients include: (1) enhancing the very small residual amounts of LPL activity that these patients may have, below the limit of detection of the assay in many cases (2) potentially enhanced activity of other lipases also involved in the metabolism and breakdown of TGs, such as hepatic lipase or endothelial lipase (Kinnunen and Ehnolm 1976), and (3) apoC-III interaction with Apolipoprotein E (apoE), an important factor in liver reuptake of lipid particles by blocking apoE-mediated uptake of lipid particles in the liver (Breyer et al. 1999), and therefore, reducing apoC-III might enhance apoE-mediated uptake of lipid particles. Volanesorsen-mediated reduction of apoC-III could be contributing to one or all of these mechanisms resulting in the observed potent and sustained reductions in TG.

Through a novel apoC-III lowering mechanism of action, volanesorsen may provide the potential to manage triglyceride levels in FCS patients.

2.3 Volanesorsen

2.3.1 Mechanism of Action

Volanesorsen is a second-generation antisense oligonucleotide (ASO) drug targeted to human apoC-III. It is complementary to a region within the 3′ untranslated region of the apoC-III messenger ribonucleic acid (mRNA) and binds to the mRNA by Watson and Crick base pairing.

The hybridization (binding) of volanesorsen to the cognate mRNA, results in the RNase H1-mediated degradation of the apoC-III mRNA, thus preventing production of the apoC-III protein. Maximal antisense-mediated reduction of target mRNA levels is typically greater than 90% of control levels in sensitive tissues (Crooke and Bennett 1996; Zhang et al. 2010). Furthermore, reduction in target mRNA levels using this approach correlates directly with a subsequent reduction in target protein levels.

2.3.2 Chemistry

Chemically, volanesorsen is a synthetic oligomer of 20 nucleotides (i.e., a 20-mer) that are connected sequentially by phosphorothioate linkages. The nucleotide sequence of volanesorsen (Figure 2) is complementary to a 20-nucleotide stretch within the 3′ untranslated region of the apoC-III mRNA transcript at base position 489-508. Structurally, the oligonucleotide has 3 regions. Two (2) of them, the 5 nucleotides at the 5′ end and the 5 nucleotides at the 3′ end, are composed of 2′-*O*-(2-methoxyethyl) (MOE)-modified ribonucleotides. These MOE-modified nucleotides confer (1) increased affinity to the target mRNA (Altmann et al. 1996; McKay et al. 1999), (2) increased resistance to exonucleases and endonucleases (thereby increasing stability in tissue) (Geary et al. 2003), and (3) amelioration of some of the high dose toxicities thereby resulting in an improved safety profile compared to first generation antisense drugs containing phosphorothioate modified oligodeoxynucleotides (DNA) (Henry et al. 2000). The third region, the central portion of the oligonucleotide, is composed of 10 oligodeoxynucleotides. This chimeric design is called a MOE-Gapmer, and volanesorsen employs this chimeric structure to enable use of the RNase H1-mechanism for antisense activity. This is because while the 2′-MOE modification confers increased stability and affinity, it does not support RNase H1 catalysis of RNA hybridized to 2′-MOE-modified nucleotides (McKay et al. 1999). This is caused by conformational changes induced in the heteroduplex by 2′-alkoxy:RNA hybrids that are not recognized by RNase H1 enzymes (Inoue et al. 1987; Monia et al. 1993). By limiting the 2′-MOE modification to nucleotides flanking the phosphorothioate oligodeoxynucleotide core, the beneficial attributes of the 2′-MOE chemistry are preserved while also retaining RNase H1 recognition.

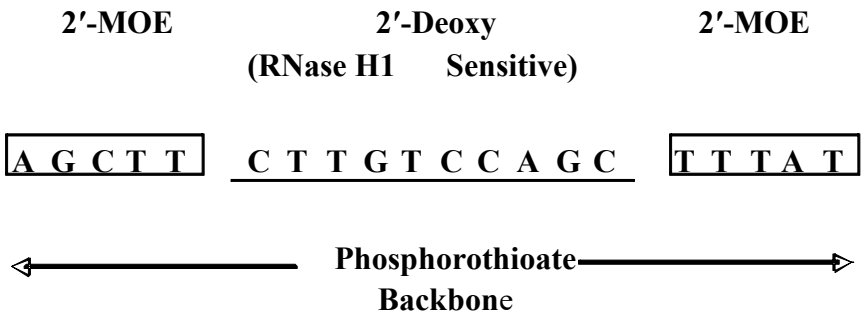


Figure 2 Design of Chimeric 2′-MOE Phosphorothioate Oligonucleotides (MOE-Gapmer). The sequence of volanesorsen is shown

2.3.3 Preclinical Experience

Inhibition of apoC-III using volanesorsen has been shown to potently reduce hepatic apoC-III mRNA as well as plasma apoC-III protein and TG in a dose- and time-dependent fashion in several species, including human apoC-III transgenic mice, and other rodent and monkey models. Treatment with volanesorsen also resulted in reduced VLDL and chylomicron TG and reduced postprandial TG in hypertriglyceridemic monkeys (Graham et al. 2013).

The pharmacokinetics (PK) and toxicity of volanesorsen have been assessed in mice, rats, and cynomolgus monkeys. General toxicity studies with volanesorsen for up to 39 weeks of treatment followed by up to a 20-week recovery period are complete. The preclinical toxicology program for volanesorsen consists of single dose safety pharmacology studies in the monkey (cardiovascular) and mouse (neurobehavioral and pulmonary assessment studies), *in vitro* and *in vivo* genetic toxicity assessment, repeat dose fertility and/or developmental reproductive toxicology studies in the mouse and rabbit and evaluation in the *in vitro* human Ether-á-go-go-related gene (hERG) assay.

Volanesorsen treatment-related findings in mice and monkeys were generally consistent with those expected for the 2′-MOE-class of ASOs. Treatment-related findings included effects consistent with drug accumulation in tissues in rodents and monkeys, species-dependent proinflammatory response in rodents and monkeys and complement activation and reductions in platelet counts in the monkey. In the mouse and monkey general toxicity studies, reduction of hepatic apoC-III mRNA (> 75%) was not associated with any findings that could be considered related to the pharmacologic inhibition of apoC-III for up to 39 weeks of treatment.

The long-term, chronic toxicology studies in rodents with volanesorsen produced a significant proinflammatory response that led to subsequent effects on the heart at high doses. The rodent species are most sensitive to the proinflammatory effects of antisense molecules. Importantly, these effects on the heart were not observed in the monkey chronic toxicity studies even at the highest doses tested where drug exposure was higher than that in rodents.

Because these changes were not observed in monkeys, the findings in the heart are considered to be rodent-specific and not relevant to humans. Nevertheless, such effects will be monitored by measurement of echocardiograms that will be included in this clinical study.

Volanesorsen caused no untoward effects in safety pharmacology studies (*in vitro* and *in vivo*) and was non-genotoxic (*in vitro* and *in vivo*). Volanesorsen had no effects on fertility or embryo/fetal development in the mouse or rabbit reproductive toxicity studies. In these studies, volanesorsen was detected in placental tissue but not in fetal tissue indicating that little, if any, drug was able to cross the placenta to reach the fetus. Reduction of apoC-III mRNA (64% in males and 47% in females) also did not affect fertility or cause untoward effects on embryo/fetal development in mice.

Detailed information concerning the preclinical studies conducted with volanesorsen can be found in the volanesorsen Investigator's Brochure.

2.3.4 Clinical Experience

Detailed information concerning the clinical studies conducted with volanesorsen can be found in the volanesorsen Investigator's Brochure. A summary is included below.

Volanesorsen has been evaluated in one Phase 1 study and two Phase 2 studies, all double blinded and placebo controlled. The total exposures comprise 99 patients and healthy volunteers administered volanesorsen from 50 to 400 mg subcutaneously up to 3 months (compared to 37 administered placebo).

All clinical trials of volanesorsen have shown large and clinically meaningful reductions in fasting plasma apoC-III and TG (~80% and 70%, respectively, mean reduction from baseline with 300 mg dose) with a very high degree of consistency of response between the different patient groups. This includes healthy volunteers, patients with moderate to severe hypertriglyceridemia not on background TG-lowering therapy, patients with moderate to severe hypertriglyceridemia on a background stable fibrate therapy (Gaudet et al. 2015), patients with FCS, and patients with T2DM.

In a Phase 2 study, 3 patients with FCS were treated with 300 mg/wk volanesorsen in an open label fashion. These patients had a mean baseline fasting TG level of 1,844 mg/dL and all 3 patients achieved TG levels below or close to 500 mg/dL during the dosing period out to Day 92 (Figure 3). Two (2) of the FCS patients had an absolute reduction in fasting TG in excess of 1,500 mg/dL (Gaudet et al. 2014).

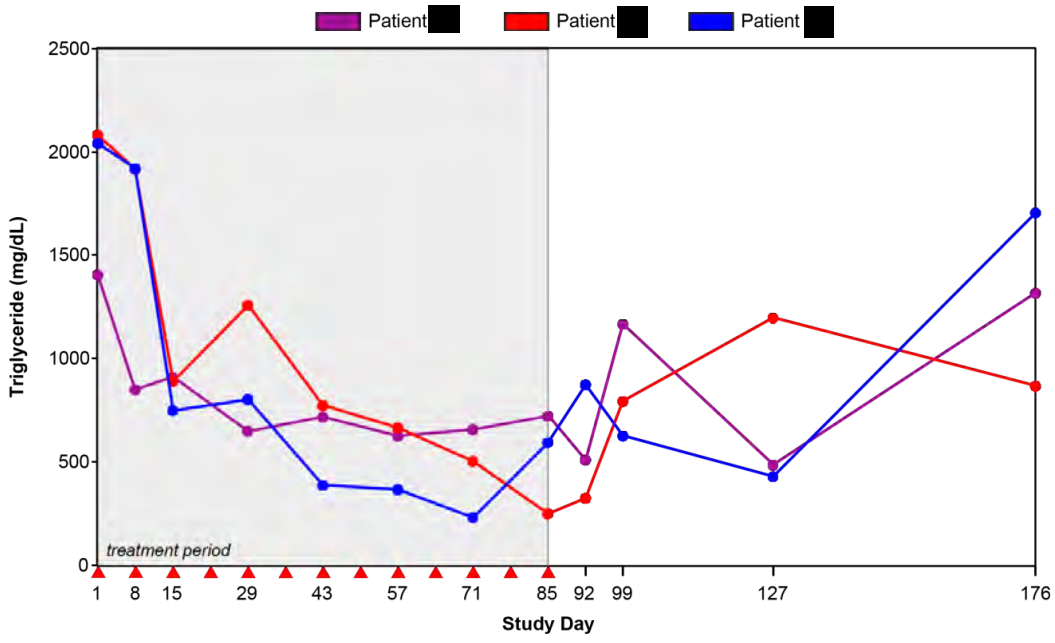


Figure 3 Fasting Triglycerides in Patients with FCS Treated with Volanesorsen

In clinical studies conducted to date volanesorsen has been well-tolerated and has shown a favorable safety profile. There has been no clinical or laboratory evidence of drug-drug interactions.

In the completed studies there have been no volanesorsen associated laboratory abnormalities suggestive of an effect on the renal (serum creatinine, proteinuria) or hepatic systems (alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin). In Phase 2 studies, there was a mild decrease of platelet count associated with volanesorsen administration that recovered in the post-treatment period and was not associated with platelet-related adverse events (AEs). In the blinded ongoing clinical trials of ISIS 304801, 2 patients of 142 dosed (as of February 29, 2016) had a decrease in platelet count to less than 50,000/mm^3 in the absence of major bleeding or clinically-relevant non-major bleeding and had Study Drug paused as per the monitoring and stopping rules for platelet counts (Section 8.6.3). Platelet counts recovered following suspension of dosing.

The most frequently observed AEs with volanesorsen were local reactions at the injection site. Local cutaneous reactions at the injection site defined as those events presenting as either pain, tenderness, erythema, pruritus or swelling occurring on the day of injection and persisting for at least 2 days were infrequent (~15% of injections), were almost always mild, resolved spontaneously, were non-progressive, and were not associated with systemic sequelae.

2.4 Rationale for Dose and Schedule of Administration

The dose and schedule selected for this study is 300 mg per week for 52 weeks. The dose of 300 mg per week is supported by both the cumulative nonclinical data available to date and the Phase 2 clinical data. In nonclinical studies, volanesorsen treatment-related effects in rodents and monkeys were consistent with drug accumulation in tissues and also include species-specific proinflammatory responses. In the monkey, the No-Observed-Adverse-Effect Level (NOAEL) was defined by the cumulative clinical pathology results and histopathology data which provide an adequate clinical margin. No nonclinical findings were considered to be related to the pharmacologic inhibition of apoC-III.

The safety data to date suggest that volanesorsen has been well-tolerated at dose levels up to 300 mg in patients with high triglycerides (including type 2 diabetes patients and administration in combination with fibrates and statins) with the most common AEs being local to the injection site and predominantly mild. A pooled analysis of safety for the Phase 2 studies did not demonstrate any clear difference in safety or tolerability between the different doses tested (100 mg, 200 mg, and 300 mg per week for 13 weeks).

Analysis of the cohorts in which volanesorsen was studied at different doses demonstrates dose-dependent pharmacology with respect to pharmacodynamic (PD) effect on the target, apoC-III, with a clear difference in the TG-lowering effect between the different doses in the 100 mg to 300 mg dose range as compared to placebo.

In addition to the nonclinical and clinical experience of volanesorsen, the dose and schedule of administration is supported by the preclinical and clinical safety experience of several other 2′-MOE-modified ASOs that have been safely administered intravenously and subcutaneously in multiple clinical studies at doses up to 1000 mg and for treatment durations that exceed 24 months (Santos et al. 2015).

3. EXPERIMENTAL PLAN

3.1 Study Design

This is an open-label extension to the Phase 3 study of volanesorsen in patients with FCS (ISIS 304801-CS6 or ISIS 304801-CS16). Up to approximately 70 patients will receive 300 mg once weekly volanesorsen for 52 weeks.

Following the Week 52 visit, patients enter a 13-week post-treatment evaluation period.

3.2 Number of Study Centers

This study will be conducted at multiple centers worldwide.

3.3 Number of Patients

Up to approximately 70 patients will be dosed.

3.4 Overall Study Duration and Follow-up

The Study will consist of the following periods:

- A qualification period of up to 2 weeks (unless approved by the Sponsor). Please refer to Section 4.1 and Appendix A.
- A 52-week treatment period during which volanesorsen will be administered as a once weekly SC injection
- A 13-week post-treatment evaluation period

Please refer to the Schedule of Procedures in Appendix A.

3.4.1 Qualification

A period of up to 2 weeks is given to complete qualification assessments outlined in the Schedule of Procedures (Appendix A).

3.4.2 Treatment

The treatment period is 52 weeks. Eligible patients will report to the Study Center for assessments at specified intervals throughout the 52-week treatment period as detailed in the Schedule or Procedures (Appendix A). During the treatment period, volanesorsen is administered by SC injection once weekly.

3.4.3 Post-Treatment

The post-treatment evaluation period is 13 weeks and consists of 2 Study Center visits on Weeks 58 and 65.

3.5 End of Study

The End-of-Study is last patient, last visit.

3.6 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will review (as needed) safety, tolerability and efficacy data collected on volanesorsen during this study. Based on its ongoing assessment of the safety and tolerability of volanesorsen, the DSMB will provide recommendations to the Sponsor for modifying, stopping or continuing the study as planned. Details on the safety assessments, frequency of review and meeting schedules are outlined in the DSMB Charter and/or the statistical analysis plan (SAP).

4. PATIENT ENROLLMENT

4.1 Qualification

Before patients may be enrolled into the study, the Sponsor requires a copy of the Study Center's written independent ethics committee/institutional review board (IEC/IRB) approval of the protocol, informed consent form, and all other patient information.

Patients or their legally acceptable representatives must sign the consent form before any study-specific procedures or evaluations related to this open label study are performed. During the qualification period, the eligibility of the patient to continue in the extension study will be determined. Final assessments from the ISIS 304801-CS6 or ISIS 304801-CS16 studies may be used for qualification. A period of up to 2 weeks after completion of the ISIS 304801-CS6 or ISIS 304801-CS16 index studies (unless approved by the Sponsor) is given to complete qualification. Qualified patients will retain the unique patient identification number that was assigned to them during the ISIS 304801-CS6 or ISIS 304801-CS16 index studies. The patient identification number will be used to identify the patient throughout the extension trial and must be used on all study documentation related to that patient. The patient identification number must remain constant throughout the extension trial.

4.2 Enrollment

Patients will be enrolled after all qualification assessments have been completed and after the Investigator has verified that they are eligible per criteria in Sections 5.1 and 5.2. No patient may begin treatment prior to enrollment.

Eligible patients will be enrolled using an Interactive Voice/Web-Response System (IXRS).

5. PATIENT ELIGIBILITY

To be eligible to participate in this study candidates must meet the following eligibility criteria within 2 weeks of Study Day 1, or at the time point specified in the individual eligibility criterion listed.

5.1 Inclusion Criteria

1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law
2. Age ≥ 18 years at time of informed consent
3. Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement. Patients who are

enrolled in ISIS 304801-CS16 must also meet the following criteria in order to enter into the Extension Study:

a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L)

b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) by documentation of at least 1 of the following:

- Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoC-II, GPIHBP1, or LMF1)
- Post heparin plasma LPL activity of ≤ 20% of normal

c. Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 study.

4. Able and willing to participate in a 65-week study

5. Satisfy 1 of the following:

a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved), abstinent*, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration.

b. Males: Surgically sterile, abstinent* or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration.

* Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception

5.2 Exclusion Criteria

1. Have any new condition or worsening of existing condition which in the opinion of the Investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study.

2. Unwilling to comply with lifestyle requirements for the duration of the study (Section 6.3).

6. STUDY PROCEDURES

6.1 Study Schedule

All required study procedures are outlined in Appendices A, B, C, and D.

6.1.1 Qualification

Please refer to Section 4.1 and Appendix A.

6.1.2 Treatment Period

The patients, Investigators, study staff, and the Sponsor will remain blinded to lipid data through the last patient's Week 13 visit of the extension study or until results from the database locks for the ISIS 304801-CS6 and ISIS 304801-CS16 index studies become available, whichever comes first.

During the treatment period, patients will report to the study center for clinic visits a minimum of 5 times during Weeks 1-52 (see Schedule of Procedures in Appendix A). Study Drug will be administered once weekly (Section 8.1). Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), AEs, concomitant medication/procedure information, lipid panel, volanesorsen plasma concentrations, immunogenicity (IM) testing, liver/spleen MRI, ECGs, echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Adverse events at the injection site should be collected as adverse events. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period and all patients will complete a daily food diary for one week prior to their quarterly visit. All blood and urine samples should be collected prior to volanesorsen administration. Blood sampling at Weeks 4, 8, 12, 16, 19, 22, 25, 29, 32, 35, 41, 44, 47, 51, and 58 may be conducted by a home healthcare nurse . Approval for study procedures to be conducted by a home healthcare nurse on other outpatient visit days will require prior approval by the Sponsor. Patients must be fasted prior to drawing all blood samples and samples drawn locally must be sent to the central laboratory for analysis. Every effort should be made to ensure the previous week's dose is given 7 days prior to a scheduled clinic visit. Dosing instructions and training will be provided to the patient where applicable.

All reasonable attempts should be made to ensure compliance with the visit schedule as outlined in Appendix A. However, in the event that a visit does not occur or is delayed, all subsequent visits should be calculated based on the time elapsed since Day 1 rather than from the date of the previous visit.

6.1.3 Pharmacokinetic (PK) Subgroup

A subgroup of patients will participate in an extended PK collection. Patients in this subgroup will have more frequent PK sampling over a 24-hour period following the first dose on Study Day 1 in order to evaluate the plasma PK parameters of volanesorsen. Patients in this subgroup will have an additional visit to the clinic, or by a home healthcare nurse, on Day 2 to collect a 24-hour post-dose blood draw after dosing on Day 1. The detailed PK sampling schedules are outlined in Appendix C.

Participation in the PK subgroup is optional for sites and patients, and consent may be withdrawn for the subgroup-specific procedures (e.g., multiple blood draws for PK) without being withdrawn from the study. If a patient withdraws consent from the subgroup procedures, he/she should remain on study and continue to follow all the non-subgroup assessments and procedures as outlined in Appendix A.

6.1.4 Post-Treatment Period

After completion of the Week 52 visit assessments, patients will enter the 13-week post-treatment evaluation period. This period consists of 2 Study Center visits on Weeks 58 and 65 as outlined in the Schedule of Procedures in Appendix A.

6.2 Additional Study Assessments

6.2.1 Laboratory Assessments

Laboratory analyte samples will be collected throughout the study.

A list of these analytes is contained in Appendix B.

6.2.2 Physical Exams and Vital Signs

Physical exams and vital signs will be performed as indicated in the Schedule of Procedures (Appendix A). Vital signs should include weight, blood pressure, pulse rate, respiratory rate and body temperature. Blood pressure and pulse rate will be recorded after the patient has been in a sitting position for at least 5 minutes. Semi-supine systolic and diastolic blood pressure should always be measured on the same arm (preferentially on the left arm). Height will be measured at the Day 1 visit.

6.2.2.1 Eruptive Xanthoma

At each visit, patients will be asked whether they have had any episodes of eruptive xanthoma since their last visit and the number/duration of the events will be recorded. Physical exams should also include skin examination for presence/resolution of eruptive xanthomas. If a patient experiences an episode of eruptive xanthoma during the study, photos of the area should be taken, if possible.

6.2.2.2 Lipemia Retinalis

If possible, lipemia retinalis will be assessed by fundus photography prior to administration of the first dose of Study Drug (for ISIS 304801-CS16 rollover patients) and repeated at Week 52. Images will be evaluated by an independent assessor, blinded to the patient's treatment assignment.

6.2.3 Echocardiography

Echocardiography for assessment of left and right ventricular function and mitral and aortic valve function will be conducted at Week 26 and Week 52 in all patients. For the purpose of assessment of treatment-emergent changes, all echocardiograms will be evaluated on an ongoing basis by an independent central reader. Results will be provided to the DSMB for their review.

6.2.4 ECG

The ECG will be recorded after the patient has been resting in a supine position for at least 5 minutes. ECGs will be performed in triplicate at Week 13, Week 26, Week 38, Week 52, and Week 65.

6.2.5 MRI

MRI of the liver and spleen will be conducted at Week 52 for all patients for whom MRI is not contraindicated, e.g., patients having metal implants.

MRIs will be conducted using standardized procedures and settings. MRIs will be read by an independent central reader to assess liver fat and liver and spleen size**.**

6.2.6 Quality of Life Assessments

All patients will complete Quality of Life Questionnaires (EQ-5D and SF-36) at Week 1, Week 13, Week 26, Week 52, and Week 65.

6.2.7 Disease Symptom Diary

All patients will complete a symptom questionnaire once a week starting at the beginning of the qualification period and continuing to the end of the post-treatment follow-up period.

6.2.8 Diet Monitoring

The diets of patients enrolled in the study will be monitored as follows:

1. All patients will be required to maintain a 7-day food diary prior to Week 1, Week 13, Week 26, Week 52, and Week 65.

2. Patients will receive diet/alcohol counseling by qualified study personnel at clinic visits throughout the course of the study. Qualified study personnel will telephone the patient to provide diet/alcohol counseling for visits that are conducted by a clinical service.

3. In addition to the 7-day food diary and the diet /alcohol counseling during clinic visits, telephone calls from a dietitian or qualified study personnel to assess as to how each patient is maintaining their diet will be conducted randomly during the treatment and post treatment follow-up periods.

6.2.9 Family History

Family history of hypertriglyceridemia and pancreatitis will be collected for each patient.

6.2.10 Lipoprotein Lipase Activity Sample Collection

Lipoprotein lipase (LPL) activity will be measured in ISIS 304801-CS16 rollover patients if needed for study qualification. In brief, fasted patients will be given a low intravenous dose of heparin. A blood sample will be drawn prior to and at 10 or 15 minutes after the heparin administration for measurement of LPL activity as per instructions provided to the Investigator.

6.3 Restriction on the Lifestyle of Patients

6.3.1 Contraception Requirements

All male patients and women of childbearing potential must refrain from sperm/egg donation and either be abstinent* or, if engaged in sexual relations of child-bearing potential, practice effective contraception from the time of signing the informed consent form until at least 13 weeks after their last dose of study treatment.

Male patients must also encourage their female partner to use effective contraception from the time of signing the informed consent until 13 weeks after the subject's last dose of study treatment.

For the purposes of this Study, women of childbearing potential are defined as any female who has experienced menarche, and who does not meet 1 of the following conditions:

- Postmenopausal: 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved
- 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Post hysterectomy

For the purposes of the study, effective contraception is defined as follows:

For male patients:

- Effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the use of condoms together with spermicidal foam/gel/film/ cream/suppository. Male patients must also encourage their female partner to use effective contraception from the time of signing the informed consent until 3 months after the patient's last dose of study treatment. Effective contraceptive for the female partner includes: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or barrier methods (female condom*, diaphragm, sponge, cervical cap) together with spermicidal foam/gel/film/cream/suppository. Male patients with partners that are pregnant must use condoms to ensure that the fetus is not exposed to the Study Drug.

For female patients:

- Using one or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or any 2 barrier methods (a combination of male or female condom* with diaphragm, sponge, or cervical cap) together with spermicidal foam/gel/film/cream/suppository.

*Note: A female condom and a male condom should not be used together as friction between the two can result in either product failing.

* Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception

6.3.2 Other Requirements

All patients will be required to fast for at least 10 hours and preferably not more than 12 hours before visits requiring fasted blood sampling.

All patients will be encouraged to follow a diet comprising ≤ 20 g fat per day during the study.

Alcohol should not be consumed during the study.

All patients will be given an instruction card that must be presented to the treating physician if a suspected case of pancreatitis occurs. The card will explain that the patient is in a clinical trial and that serum lipase and/or amylase measures should be done in order to adjudicate the event, based on Atlanta Classification (Banks et al. 2013). If serum or amylase activity is less than 3 x upper limit of normal (ULN), imaging, preferably contrast-enhanced computed tomography, should be considered to confirm the diagnosis of acute pancreatitis per the Atlanta Criteria.

7. STUDY DRUG

7.1 Volanesorsen Description

Volanesorsen drug product (ISIS 304801) characteristics are listed in Table 1.

Volanesorsen (ISIS 304801) is contained in glass prefilled syringes (PFS). Volanesorsen and its storage and preparation instructions will be provided by the Sponsor or designee. Volanesorsen must be stored securely at 2° to 8° C and be protected from light.

Table 1 Volanesorsen (ISIS 304801) Characteristics

Strength	200 mg/mL
Volume/Formulation	1.5 mL solution per PFS
Dose	300 mg once weekly
Route of Administration	SC

7.2 Packaging and Labeling

The Sponsor will provide the Investigator with packaged volanesorsen labeled (ISIS 304801) in accordance with specific country regulatory requirements.

7.3 Study Drug Accountability

The study staff is required to document the receipt, dispensing, and return/destruction of volanesorsen provided by the Sponsor. The Study Center must return all unused volanesorsen to the Sponsor or designee. All used syringes must be disposed of as per the site's hazardous waste destruction policy.

8. TREATMENT OF PATIENTS

8.1 Volanesorsen Administration

For each individual patient, volanesorsen will be administered subcutaneously as a single 1.5 mL injection once weekly for Weeks 1-52.

Patients should receive 1 dose per week, with weeks always defined relative to Study Day 1. For example if a patient receives the first dose on a Monday, subsequent doses should be given on Mondays, if possible. If a patient misses an injection, or if dosing on the usual day is not possible, the patient can reschedule the injection provided that 2 doses are administered at least 2 days apart.

Every effort should be made to ensure the previous week's dose is given 7 days prior to a scheduled clinic visit.

Please refer to the Study Drug Manual provided by the Sponsor for more detailed instructions for volanesorsen preparation and administration.

8.2 Other Protocol-Required Drugs

There are no other protocol-required drugs (Section 6.2.5).

8.3 Other Protocol-Required Treatment Procedures

There are no other protocol required treatment procedures for this study.

8.4 Treatment Precautions

There are no specific treatment precautions required for this study.

8.5 Safety Monitoring Rules

Please refer also to the 'Guidance for Investigator' section of the Investigator's Brochure.

For the purposes of safety monitoring baseline is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 (e.g., qualification assessments or assessments from the final visits of ISIS 304801-CS6 and ISIS 304801-CS16 index studies if used for qualification).

In addition to the standard monitoring of clinical safety parameters, the following guidelines are provided for the monitoring of selected parameters chosen based on preclinical and clinical observations.

Confirmation Guidance: At any time during the study (Treatment or Post-Treatment Periods), the initial clinical laboratory results meeting the safety monitoring or stopping criteria presented below **must be confirmed** by performing measurements (ideally in the same laboratory that performed the initial measurement) on new specimens. All new specimen collections should take place as soon as possible (ideally within 3 days of the initial collection). For stopping rules, if the initial laboratory result is observed during the Treatment Period, the results from the retest **must be available** prior to administering the next dose of volanesorsen.

In addition to the safety monitoring parameters listed below, the Sponsor may request confirmation of additional lab values.

Re-dosing Guidance: Patients with initial laboratory test values that reach a stopping rule must not be re-dosed until the re-test results are available. In general, patients who do not meet the stopping rules based upon retest may continue dosing. However, the Investigator and the Sponsor Medical Monitor (or appropriately qualified designee) should confer as to whether additional close monitoring of the patient is appropriate. If any of the stopping criteria described below (refer to Sections 8.6.1 to 8.6.3) are met, the patient will be permanently discontinued from further treatment with volanesorsen, evaluated fully as outlined below and in consultation with the Sponsor Medical Monitor or appropriately qualified designee, and will be followed up in accordance with Section 8.8 of the protocol.

8.5.1 Safety Monitoring for Liver Chemistry Tests

The following rules are adapted from the draft guidance for industry, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," issued by the U.S. Department of Health and Human Services, Food and Drug Administration, July 2009. For a definition of Baseline please refer to guidance in Section 8.5 above.

In the event of an ALT or AST measurement that is > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) at any time during the study (Treatment or Post-Treatment Period), the initial measurement(s) should be confirmed as described above. Additional confirmatory measurements should also be performed if ALT or AST levels increase to 5 x ULN.

Frequency of Repeat Measurements: Patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) should have their liver chemistry tests (ALT, AST, alkaline phosphatase (ALP), international normalized ratio (INR) and total bilirubin) retested at least once-weekly until ALT and AST levels become ≤ 1.2 x ULN or 1.2 x baseline value if the baseline value was > ULN.

Further Investigation into Liver Chemistry Elevations: For patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), the following evaluations should be performed:

1. Obtain a more detailed history of symptoms and prior and concurrent diseases
2. Obtain further history for concomitant drug use (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
3. Obtain a history for exposure to environmental chemical agents and travel
4. Serology for viral hepatitis (HAV IgM, HBsAg, HCV antibody, CMV IgM, and EBV antibody panel)
5. Serology for autoimmune hepatitis (e.g., antinuclear antibody [ANA])

Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic CT or MRI scans, may be performed at the discretion of the Investigator, in consultation with the Sponsor Medical Monitor. Repetition of the above evaluations should be considered if a patient's ALT and/or AST levels reach 5 x ULN.

8.5.2 Safety Monitoring for Platelet Count Results

In the event of any significant fall in platelet count, or if the absolute platelet count is 75,000/mm^3 or less, then the patient's platelet counts should be monitored more frequently. The frequency of monitoring and additional lab tests will be determined by the Sponsor Medical Monitor or designee in consultation with the Investigator.

8.5.3 Safety Monitoring for Minor Bleeding Events

Minor bleeding events are those that do not fulfill the criteria for major bleeding or clinically-relevant, non-major bleeding events (which are defined in Section 8.6.3), for example excess bruising, petechiae, gingival bleeding on brushing teeth. If a minor bleeding event occurs, the Investigator must notify the Sponsor Medical Monitor and additional testing of coagulation parameters activated partial thromboplastin time (aPTT), prothrombin time (PT), INR and platelet count should be performed.

8.5.4 Safety Monitoring for Constitutional Symptoms

Patients will be instructed to promptly report any signs of symptoms of fever or constitutional symptoms that may arise during the study and the Investigator should closely evaluate all potential causes, including concomitant illness. Patients that experience persistent constitutional symptoms should be discussed with the Sponsor Medical Monitor or designee to determine whether additional monitoring or laboratory tests are required.

8.5.5 Safety Monitoring for LDL-C Elevations

Beginning at Week 13, laboratory alerts will be in place to notify the Investigator if a patient has a low-density lipoprotein-cholesterol (LDL-C) > 160 mg/dL (> 130 mg/dL for patients with T2DM) on 2 consecutive visits. If this occurs, LDL-C values for this patient will be unblinded for the remainder of the study and the Investigator will be encouraged to initiate/adjust treatment to lower LDL-C according to country-specific guidelines (e.g., initiate statin therapy or increase the statin dose for patients who are already on treatment).

8.5.6 Safety Monitoring for Insulin, Oral Antidiabetic Medication and Glucose

All patients on insulin will monitor their glucose levels with a glucometer as per standard practice guidelines and bring their glucometer or glucometer log printout to every clinic visit. In addition, patients who are not on insulin (e.g., patients with type 2 diabetes), but use a glucometer should also bring their glucometer and/or glucometer log printout to every clinic visit.

- The Investigator or delegate will review the glucometer reading or printout at every clinic visit to evaluate if fasting pre-breakfast self-monitored plasma glucose values exceed threshold values as per the Safety Monitoring Rules for Hyperglycemia below.

All diabetic patients will note any changes in their insulin dose and /or oral antidiabetic therapy, as well as any hypoglycemic episode they may experience.

- The Investigator or delegate will ask patients at every clinic visit if they made changes in their insulin dose or oral antidiabetic therapy, and if they experienced a hypoglycemic episode.
  - Patients will be instructed on the monitoring and management of hypoglycemic episodes at each visit.
  - Documented symptomatic hypoglycemic episodes should be captured as adverse events in the adverse event CRF. Documented symptomatic hypoglycemia is defined as typical hypoglycemia symptoms accompanied by measured plasma glucose ≤ 70 mg/dL (≤ 3.9 mmol/L.
  - Any changes in insulin dose or oral antidiabetic therapy should be captured into the Concomitant Medication CRF.

8.5.7 Safety Monitoring for Documented Severe Hypoglycemia

A **documented severe hypoglycemic event** is defined as 1 in which the patient requires assistance of another person to obtain treatment for the event and has a plasma glucose level ≤ 70 mg/dL (≤ 3.9 mmol/L). The rescue treatment of hypoglycemia may include IV glucose or buccal or intramuscular glucagon.

The definition of severe symptomatic hypoglycemia includes all episodes in which neurological impairment was severe enough to prevent self-treatment and which were thus thought to place patients at risk for injury to themselves or others. Note that "requires assistance" means that the patient could not help himself or herself. Someone being kind that assists spontaneously the patient when not necessary does not qualify as "requires assistance."

Severe hypoglycemia will be qualified as a SAE only if it fulfills SAE criteria.

If a patient presents with symptoms of hypoglycemia, the Investigator will need to take immediate action to confirm the patient's glucose level and treat the patient accordingly.

The experience of hypoglycemia may vary greatly from patient to patient. However, there are certain classical signs and symptoms, of which patients should be aware as a clue that their blood glucose may be low. Common symptoms include headache, heart pounding, confusion, disorientation, numbness or tingling, pale skin, shakiness or tremulousness, increased appetite, anxiousness or nervousness, lightheadedness or dizziness, sweating, and weakness. Coma could occur if blood sugar correction is not performed.

If patients suspect they might be having a hypoglycemia reaction, they should check their blood glucose using their meters as soon as possible, before treatment if possible, provided they feel it is safe to do so. If there is doubt about safety they should treat the event first, using some sugar, milk, or juice for example, then obtain and record a blood glucose value as soon as possible thereafter. The time and nature of treatment should be noted, and especially if any blood glucose result was before or after treatment. It would be helpful for the patient to note if a contributory factor (e.g., missed or reduced meals, unaccustomed physical activity) occurred earlier in the day of the event.

8.5.8 Safety Monitoring for Hyperglycemia

Upward dose titration and/or addition of any other anti-hyperglycemic agent(s) will not be allowed during the course of the study, unless specific threshold values are met at Week 13 or later and confirmed on subsequent testing (ideally within 1 week of the initial test).

HbA1c is monitored every 3 months throughout the study. In addition, patients on insulin should self-monitor their plasma glucose (SMPG) routinely on a glucometer as per practice guidelines. If a fasting pre-breakfast SMPG value exceeds the specific glycemic limit, the patient should check it again on the following 2 days. If all the fasting pre-breakfast values on 3 consecutive days exceed the specific limit, the patient should contact the Investigator and an unscheduled central laboratory FPG measurement and HbA1c should be performed.

The threshold values are defined as:

- FPG > 270 mg/dL (15.0 mmol/L)
- HbA1c > 9% (for patients with baseline HbA1c < 8% and HbA1c increase of more than 1% from baseline (for patients with baseline HbA1c ≥ 8 and < 9%)

In case of confirmed FPG/HbA1c above the threshold value, the Investigator should ensure that no reasonable explanation exists for insufficient glucose control and in particular that:

- Plasma glucose was actually measured in the fasting condition (i.e., after at least 10 hours fast)
- Absence of intercurrent disease which may jeopardize glycemic control. In case of an emergency (e.g., surgery, infection), the Investigator can take appropriate measures for glycemic control
- Compliance to treatment is appropriate
- Compliance to diet and lifestyle is appropriate

If any of the above can reasonably explain the insufficient glycemic control, the Investigator should consider the following:

- Investigation and treatment of intercurrent disease (to be reported in adverse event (AE)/concomitant medication parts of the e-CRF)
- Stress on the absolute need to be compliant to treatment
- Organize a specific interview with a Registered Dietician or other qualified nutrition professional and stress on the absolute need to be compliant to diet and lifestyle recommendations

A FPG/HbA1c follow-up assessment should be arranged after appropriate action has been taken. If none from the above-mentioned reasons can be found, or if appropriate action fails to decrease FPG/HbA1c under the threshold values, additional medication may be introduced at the Investigator's discretion and according to local guidelines after discussion with the Sponsor Medical Monitor.

8.5.9 Acute Pancreatitis

If a patient has an episode of acute pancreatitis, dosing with Study Drug should be suspended temporarily until the patient is clinically stable. The suitability of the patient for continued dosing and the need for any modification to treatment schedule (refer to Section 8.7) will be determined by the Investigator in consultation with the Study Medical Monitor.

8.6 Stopping Rules

For the purposes of stopping rules baseline is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1.

8.6.1 Stopping Rules for Liver Chemistry Elevations

In the event of laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor,** dosing of a patient with volanesorsen will be stopped permanently; values that are not confirmed due to failure to retest or missing lab values will be presumed confirmed:

1. ALT or AST > 8 x ULN, which is confirmed
2. ALT or AST > 5 x ULN, which is confirmed and persists for ≥ 2 weeks
3. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed **and** total bilirubin > 2 x ULN or INR > 1.5
4. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed, and the new appearance (i.e., onset coincides with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> ULN) felt by the Investigator to be potentially related to hepatic inflammation

8.6.2 Stopping Rules for Renal Function Test Results

In the event of a persistent elevation that is observed over 2 consecutive weeks, for any of the 3 criteria below, dosing of a patient with volanesorsen may be stopped temporarily:

1. Serum creatinine increase that fulfill all of the following criteria: ≥ 0.3 mg/dL (26.5 µmol/L) and ≥ 40% above baseline creatinine values and > ULN
2. Proteinuria, dipstick 2 + (confirmed by dipstick retest and then further confirmed by a quantitative total urine protein measurement of > 1.0 g/24-hour)
3. Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault ≤ 40 mL/min that is confirmed by a 24-hour urine collection

The possible dosing re-initiation or follow-up schedule for any events meeting either of these criteria will be determined by the Investigator **in consultation with** the Sponsor Medical Monitor or designee.

8.6.3 Stopping Rules for Platelet Count Results

In the event of a platelet count less than 50,000/mm^3 that is associated with major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with volanesorsen will be stopped permanently. The follow-up schedule for any events meeting this stopping criterion will be determined by the Investigator in consultation with the Sponsor Medical Monitor.

In the event of a platelet count less than 50,000/mm^3, and in the absence of major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with volanesorsen should be suspended temporarily until the platelet count has recovered to ≥ 100,000/mm^3. The suitability of the patient for continued dosing and the need for any modification to treatment schedule (refer to Section 8.7) will be determined by the Investigator in consultation with the Study Medical Monitor and will be based on factors such as the original rate of decline in the patient's platelet count, whether any bleeding events were experienced by the patient, and the speed of recovery of platelet count upon holding of dosing.

If after the first dosing re-challenge the platelet count again falls below 50,000/mm^3, then dosing of the patient must be held until the platelet count again returns to at least 100,000/mm^3. The suitability of the patient for continued dosing and the need for any further modification to treatment schedule or dose (refer to Section 8.7) will be re-examined by the Investigator in consultation with the Study Medical Monitor based on (at least) the factors mentioned above.

If after the second re-challenge the platelet count falls below 50,000/mm^3 and is subsequently confirmed (see Section 8.5), dosing with volanesorsen will be stopped permanently. The follow-up schedule for any events meeting this stopping criterion will be determined by the Investigator in consultation with the Study Medical Monitor.

Definition of Major Bleeding Events (Schulman et al. 2005):

- Fatal bleeding, and/or
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarterial or pericardial, or intramuscular with compartment syndrome, and/or
- Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more within 24 hours, or leading to transfusion of 2 or more units of whole or red cells

Definition of Clinically-Relevant, Non-Major Bleeding Events (Schulman et al. 2005):

1. Multiple-source bleeding
2. Spontaneous hematoma > 25 cm^2
3. Excessive wound hematoma (not injection site related)
4. Macroscopic hematuria (spontaneous or lasting > 24 hours if associated with an intervention)

5. Spontaneous rectal bleeding; epitasis, gingival bleeding, hemoptysis, hematemesis

6. Bleeding after venipuncture for > 5 minutes

8.7 Adjustment of Dose Frequency

Dose adjustments, including dose interruptions, and/or decreasing the dose frequency will be allowed for safety and tolerability. Any proposed adjustment to treatment schedule must be discussed with, and approved by, the Study Medical Monitor prior to initiation. Up to 2 adjustments in the treatment schedule may be allowed for patients that are unable to tolerate the once weekly dose (for example if platelet counts fall below 50,000/mm^3 as described in Section 8.6.3). If the patient remains stable after adjustment, they may be cautiously returned to the original once weekly regimen after consultation with the Study Medical Monitor.

Patients may be dose paused in response to AEs after consultation with Study Medical Monitor.

8.8 Discontinuation of Study Treatment

A patient must permanently discontinue study treatment for any of the following:

- The patient becomes pregnant. Report the pregnancy according to instructions in Section 9.5.4
- The patient withdraws consent
- The patient experiences an AE that necessitates permanent discontinuation of study treatment
- The patient develops laboratory test abnormalities that meet any of the stopping rules listed in Section 8.6

The reason for discontinuation of study treatment must be recorded in the CRF and source documentation.

8.8.1 Follow-up Visits for Early Termination from Treatment Period

Any patient who discontinues early from the Treatment Period should be strongly encouraged to attend applicable landmark visits at Weeks 12, 13, 25, 26, and 51, 52 (calculated based on the time elapsed since Day 1) to collect fasting lipid panels and conduct safety assessments in accordance with the schedule of procedures in Appendix A. Any patient who discontinues treatment after Week 44 should also be strongly encouraged to attend a final follow-up visit (Week 65 visit assessments) approximately 13 weeks after their last dose of Study Drug, in addition to the applicable landmark visits.

If the patient declines or is unable to participate in the above, an early termination (ET) visit (Week 52 visit assessments) should be performed at the time of withdrawal, at a minimum, and ideally within 2 weeks from the last dose of Study Drug.

8.8.2 Follow-up Visits for Early Termination from Post-Treatment Follow-up Period

The patient who requests to withdraw from the study during the Post-Treatment Follow-up Period should be encouraged to undergo a final follow-up visit (Week 65, see Appendix A) prior to leaving the study.

If a patient withdraws due to an AE at any time during the study, the Investigator should arrange for the patient to have appropriate follow-up until the AE has resolved or stabilized.

8.9 Withdrawal of Patients from the Study

Patients must be withdrawn from the study for any of the following:

- Withdrawal of consent
- The patient is unwilling or unable to comply with the protocol

Other reasons for withdrawal of patients from the study might include:

- At the discretion of the Investigator for medical reasons
- At the discretion of the Investigator or Sponsor for noncompliance
- Significant protocol deviation

All efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information, including the reason for withdrawal from study, must be recorded in the CRF.

Any patient who withdraws consent to participate in the study will be removed from further treatment and study observation immediately upon the date of request. These patients should be encouraged to complete the ET study procedures and observations at the time of withdrawal (see Section 8.8 and Appendix A).

For patients withdrawn for reasons other than withdrawal of consent every effort should be made to complete the early termination study procedures and observations at the time of withdrawal (see Section 8.8 and Appendix A).

8.10 Concomitant Therapy and Procedures

The use of concomitant therapies or procedures defined below must be recorded on the patient's CRF. AEs related to administration of these therapies or procedures must also be documented on the appropriate CRF.

8.10.1 Concomitant Therapy

A concomitant therapy is any non-protocol specified drug or substance (including over-the-counter medications, herbal medications and vitamin supplements) administered between signing informed consent and completion of the post-treatment follow-up period. All concomitant medications/treatments and significant non-drug therapies (including supplements and assistive devices) received by a patient, including changes in the patient's current medications, must be

recorded in the patient's source documents and CRF. Patients taking over the counter (OTC) omega-3 fatty acids should make every effort to remain on the same brand throughout the study.

Allowed Concomitant Therapy

Any medications deemed necessary by the Investigator are allowed except those listed in the disallowed concomitant therapy.

Disallowed Concomitant Therapy

No lipid lowering therapies (e.g., fibrates, niacin, fish oil or other products containing omega-3 fatty acids [including OTC preparations]), -glucagon-like peptide-1 (GLP-1) agonists, Glybera, or systemic corticosteroids may be started or adjusted after baseline qualification. Doses of existing oral anti-diabetic medication, oral contraceptives, hormone replacement therapy, anticoagulants, or drugs or dietary supplements with potential lipid-altering effects should not be adjusted. Study patients are prohibited from receiving other experimental agents during the study. This includes marketed agents at experimental dosages that are being tested for the treatment of hypertriglyceridemia.

Patients should consult with the Site Investigator or designee prior to initiating any new medication, including non-prescription or herbal compounds or any other non-drug therapy.

8.10.2 Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between signing of informed consent and Week 65 visit.

Disallowed Concomitant Procedure

Plasma apheresis is not allowed during the study.

8.11 Treatment Compliance

Compliance with treatment dosing is to be monitored and recorded by Study Center staff. The Study Center staff is required to document the receipt, dispensing, and return/destruction of volanesorsen. Patients that are self-administering volanesorsen at home must record treatment in a dosing diary that will be reviewed periodically by Study Center staff and the Clinical Monitor.

9. SERIOUS AND NON-SERIOUS ADVERSE EVENT REPORTING

9.1 Sponsor Review of Safety Information

Safety information will be collected, reviewed, and evaluated by the Sponsor in accordance with the Safety Management Plan throughout the conduct of the clinical trial.

9.2 Regulatory Requirements

The Sponsor is responsible for regulatory submissions and reporting to the Investigators of serious adverse events (SAEs) including suspected unexpected serious adverse reactions (SUSARs) per the International Conference on Harmonization (ICH) guidelines E2A and ICH

E6. Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines.

Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) will be notified of any SAE according to applicable regulations. The Independent DSMB will be notified of any SAE as specified in the DSMB charter.

In addition to the Investigator's assessment of relatedness, the Sponsor or designee will evaluate the available information and perform an independent assessment of relatedness. While the Sponsor may upgrade an Investigator's decision it is not permissible to downgrade the Investigator's opinion for the purposes of determining whether the SAE meets the definition of a SUSAR.

The following table identifies the SAEs that the Sponsor or designee will not report on an individual basis in an expedited manner because they are anticipated to occur in the study population independent of volanesorsen exposure. The Investigator still has the responsibility to report all SAEs to the Sponsor as described in Sections 9.4.1 to 9.4.3.5.

Table 2 Expected Event for the Protocol Defined Population by Preferred Term and the Expected Incidence

Preferred Term	Expected Incidence in the Protocol Defined Population (Gaudet et al. 2010 and 2013)
Pancreatitis associated events including the PTs of hereditary pancreatitis, pancreatitis, pancreatitis acute, pancreatitis chronic, pancreatitis necrotizing, pancreatitis relapsing	0.2-0.35 events per patient-year

Fatal pancreatitis associated events will be considered as unexpected and are reportable. The Sponsor and DSMB will monitor non-fatal pancreatitis associated SAEs using the incidence rate of the event compared to the rate expected in a non-volanesorsen exposed population. If the aggregate analysis indicates that an event is occurring significantly more frequently or at a greater severity than expected, then the event will be reported.

SAEs not specified in the table will be evaluated on case by case basis to determine whether there is a reasonable possibility that the drug caused the event. If the event is considered by the Sponsor or designee to meet the definition of a SUSAR the event will be reported.

9.3 Definitions

9.3.1 Adverse Event

An adverse event is any unfavorable and unintended sign (including a clinically-significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the study or use of investigational drug product, whether or not the AE is considered related to the investigational drug product.

9.3.2 Adverse Reaction and Suspected Adverse Reaction

An adverse reaction is any adverse event caused by volanesorsen.

A suspected adverse reaction is any adverse event for which there is a reasonable possibility that volanesorsen drug caused the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

9.3.3 Serious Adverse Event (SAE)

A serious adverse event is any adverse event that in the view of either the Investigator or Sponsor, meets any of the following criteria:

- Results in death
- Is life threatening: that is, poses an immediate risk of death at the time of the event

An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Hospitalization is defined as an admission of greater than 24 hours to a medical facility and does not always qualify as an AE
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly or birth defect in the offspring of the patient (whether the patient is male or female)
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

9.4 Monitoring and Recording Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the study (i.e., before informed consent) should be recorded as Medical History and not recorded as AEs unless the pre-existing condition worsened. The Investigator should always group signs and symptoms into a single term that constitutes a **single unifying diagnosis** if possible.

9.4.1 Serious Adverse Events

In the interest of patient safety, and in order to fulfill regulatory requirements**,** all SAEs (regardless of their relationship to volanesorsen) should be reported to the Sponsor or designee

within 24 hours of the Study Center's first knowledge of the event. The collection of SAEs will begin after the patient signs the informed consent form and stop at the end of the patient's follow-up period which is defined as the Week 65 visit. When the Investigator is reporting by telephone, it is important to speak to someone in person versus leaving a message. An Initial Serious Adverse Event Form should be completed and a copy should be faxed to the Sponsor or designee.

Detailed information should be actively sought and included on Follow-Up Serious Adverse Event Forms as soon as additional information becomes available. All SAEs will be followed until resolution. SAEs that remain ongoing past the patient's last protocol-specified follow-up visit will be evaluated by the Investigator and Sponsor. If the Investigator and Sponsor agree the patient's condition is unlikely to resolve, the Investigator and Sponsor will determine the follow-up requirement.

9.4.2 Non-Serious Adverse Events

The recording of non-serious AEs will begin after the patient signs the informed consent form and will stop at the end of the patient's follow-up period, which is defined as the Week 65 visit. The Investigator will monitor each patient closely and record all observed or volunteered AEs on the Adverse Event Case Report Form.

9.4.3 Evaluation of Adverse Events (Serious and Non-Serious)

The Investigator's opinion of the following should be documented on the Adverse Event Case Report Form:

9.4.3.1 Relationship to the Study Drug

The event's relationship to volanesorsen is characterized by 1 of the following:

- **Related:** There is clear evidence that the event is related to the use of volanesorsen e.g., confirmation by positive re-challenge test
- **Possible:** The event cannot be explained by the patient's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and volanesorsen administration
- **Unlikely/Remote:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to volanesorsen administration and/or exposure suggests that a causal relationship is unlikely (For reporting purposes, Unlikely/Remote will be grouped together with Not Related)
- **Not Related:** The event can be readily explained by the patient's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and volanesorsen

9.4.3.2 Severity

The severity of AEs and SAEs will be graded based on criteria from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010 (refer to Appendix D). Any AE not listed in Appendix D will be graded as follows:

- **Mild:** The event is easily tolerated by the patient and does not affect the patient's usual daily activities
- **Moderate:** The event causes the patient more discomfort and interrupts the patient's usual daily activities
- **Severe:** The event is incapacitating and causes considerable interference with the patient's usual daily activities

If the event is an SAE, then all applicable seriousness criteria must be indicated (criteria listed in Section 9.3.3).

9.4.3.3 Action Taken with Volanesorsen

Action taken with volanesorsen due to the event is characterized by 1 of the following:

- **None:** No changes were made to volanesorsen administration and dose
- **Permanently Discontinued:** Volanesorsen was discontinued and not restarted
- **Temporarily Interrupted, restarted – same dose:** Dosing was temporarily interrupted or delayed due to the AE and restarted at the same dose
- **Reduced schedule:** Dosing frequency was reduced

9.4.3.4 Treatment Given for Adverse Event

Any treatment (e.g., medications or procedures) given for the AE should be recorded on the Adverse Event Case Report Form (treatment should also be recorded on the concomitant treatment or ancillary procedures CRF as appropriate).

9.4.3.5 Outcome of the Adverse Event

If the event is a non-serious AE then the event's outcome is characterized by 1 of the following:

- **AE Persists:** Patient terminates from the trial and the AE continues
- **Recovered:** Patient recovered completely from the AE
- **Became Serious:** The event became serious (the date that the event became serious should be recorded as the Resolution Date of that AE and the Onset Date of the corresponding SAE)
- **Change in Severity** (if applicable): AE severity changed

If the event is a SAE then the event's outcome is characterized by 1 of the following:

- **Ongoing:** SAE continuing
- **Persists (as non-serious AE):** Patient has not fully recovered but the event no longer meets serious criteria and should be captured as an AE on the non-serious AE eCRF (the SAE resolution date should be entered as the date of onset of that AE)
- **Recovered:** Patient recovered completely from the SAE (the date of recovery should be entered as the SAE resolution date)
- **Fatal:** Patient died (the date of death should be entered as the SAE resolution date)

9.4.4 Adjudication Committees

All SAEs that occur during the study that are consistent with a major acute cardiovascular event (MACE) will be adjudicated by a blinded, independent committee as outlined in the MACE Adjudication Charter.

All AEs and SAEs that occur during the study that are consistent with an event of acute pancreatitis will be adjudicated by a blinded, independent committee according to the Atlanta classification of acute pancreatitis (Banks et al. 2013) and as outlined in the Pancreatitis Adjudication Charter. In addition, data for prior episodes of acute pancreatitis or suspected pancreatitis will be collected by review of each patient's medical chart and these events will also be adjudicated.

9.5 Procedures for Handling Special Situations

9.5.1 Abnormalities of Laboratory Tests

Clinically-significant abnormal laboratory test results may, in the opinion of the Investigator, constitute or be associated with an AE. Examples of these include abnormal laboratory results that are associated with symptoms, or require treatment, e.g., bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac arrhythmias due to hyperkalemia. Whenever possible, the underlying diagnosis should be listed in preference to abnormal laboratory values as AEs. Clinically-significant abnormalities will be monitored by the Investigator until the parameter returns to its baseline value or until agreement is reached between the Investigator and Sponsor Medical Monitor. Laboratory abnormalities deemed not clinically-significant (NCS) by the Investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator should not be deemed NCS on the laboratory sheet.

The Investigator is responsible for reviewing and signing all laboratory reports. The signed clinical laboratory reports will serve as source documents and should include the Investigator's assessment of clinical significance of out of range/abnormal laboratory values.

9.5.2 Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the patient is hospitalized; the Study Center must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the patient's consent to participate in the study
- The condition that required the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the patient's consent to participate in the study and the timing of the procedure or treatment
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission

9.5.3 Dosing Errors

Volanesorsen dosing errors should be documented as Protocol Deviations. A brief description should be provided in the deviation, including whether the patient was symptomatic (list symptoms) or asymptomatic, and the event accidental or intentional.

Dosing details should be captured on the Dosing Case Report Form. If the patient takes a dose of volanesorsen that exceeds protocol specifications and the patient is symptomatic, then the symptom(s) should be documented as an AE and be reported per Section 9.4.

Should an overdose occur, the Investigator or designee should refer to the Guidance to Investigator's section of the Investigator's Brochure and contact the Sponsor or designee within 24 hours.

9.5.4 Contraception and Pregnancy

Male patients and female patients of childbearing potential must continue to use appropriate contraception with their partners, or refrain from sexual activity, as described in Section 6.3.1.

If a patient becomes pregnant or a pregnancy is suspected, or if a male patient makes or believes that he has made someone pregnant during the study, then the Study Center staff must be informed immediately. An Initial Pregnancy Form should be submitted to the Sponsor or designee **within 24 hours** of first learning of the occurrence of pregnancy. Follow-up information including delivery or termination is reported on Follow-up Pregnancy Forms and reported within 24 hours.

Payment for all aspects of obstetrical care, child or related care will be the patient's responsibility.

Female patients: If a suspected pregnancy occurs while on the study (including follow-up), a pregnancy test will be performed. The patient with a confirmed pregnancy will be immediately withdrawn from treatment with volanesorsen. However, the patient will be encouraged to complete the post-treatment follow-up portion of the study to the extent that study procedures do not interfere with the pregnancy. Regardless of continued study participation, the study physician will assist the patient in getting obstetrical care and the progress of the pregnancy will be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the Study Center and Sponsor may require access to the mother and infant's medical records for an additional 8 weeks after birth.

Male patients: The progress of the pregnancy in a male patient's partner should be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, **the Study Center and Sponsor may request access to the mother and infant's medical records for an additional 8 weeks after birth**. Follow-up will be performed to the extent permitted by applicable regulations and privacy considerations.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints

For fasting lipid measurements, the values at Month 3 analysis time point are defined as the average of Week 12 (Day 78) and Week 13 (Day 85) fasting assessments, the values of Month 6 analysis time point is at the end of Month 6 are defined as the average of Week 25 (Day 169) and Week 26 (Day 176) fasting assessments, and the values at the Month 12 analysis time point are defined as the average of Week 51 (Day 351) and Week 52 (Day 358) fasting assessments.

10.1.1 Efficacy Endpoints

- Percent change and absolute change from baseline in fasting TG
- Frequency and severity of patient reported abdominal pain during the treatment period
- Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-HDL-C, apoB, HDL-C, apolipoprotein A-1 (apoA-1), VLDL-C, and LDL-C
- Percent change from baseline in fasting total apolipoprotein C-III
- Quality of Life questionnaires (EQ-5D, SF-36)
- Adjudicated acute pancreatitis event rate
- Other symptoms: eruptive xanthoma, lipemia retinalis

10.1.2 Safety Endpoints

- Adverse events including adjudicated events of pancreatitis and MACE
- Vital signs and weight
- Physical examinations
- Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis)
- Echocardiography
- Electrocardiograms (ECGs)
- Use of concomitant medications
- MRIs

10.2 Sample Size

No sample size calculations were performed as this is an extension study to the double-blind, placebo-controlled ISIS 304801-CS6 and ISIS 304801-CS16 studies. Approximately 70 patients may be eligible to enroll into this study.

10.3 Populations

Full Analysis Set (FAS): All patients who are enrolled and have a baseline TG assessment. The FAS represents the practically-feasible intent-to-treat (ITT) population as delineated in ICH Guideline E9.

Per Protocol Set (PPS): Subset of the FAS who received 9 of first 13 scheduled doses of volanesorsen and with no significant protocol deviations that would be expected to affect efficacy and PD assessments. The detailed criteria will be specified and finalized prior to the final database lock.

Safety Set: All patients who are enrolled and receive at least 1 dose of volanesorsen.

PK Population: All patients who are enrolled, receive at least 1 dose of volanesorsen, and have at least 1 evaluable PK sample collected, analyzed, and reported.

10.4 Definition of Baseline

Definitions of baseline are given below for the purposes of the final analysis.

For fasting lipid measurements, 2 baselines are defined for each patient: ISIS 304801-CS6 or ISIS 304801-CS16 index study baseline and the baseline in this open label study, which is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 (e.g., qualification assessments or assessments from final visit of the ISIS 304801-CS6 or ISIS 304801-CS16 index studies if used for qualification).

For other measurements, baseline for patients on active treatment in the ISIS 304801-CS6 or ISIS 304801-CS16 index study will be the ISIS 304801-CS6 or ISIS 304801-CS16 index study baseline. For patients on placebo in the ISIS 304801-CS6 or ISIS 304801-CS16 index study, baseline for safety will be the last non-missing assessment prior to the first dose of Study Drug.

10.5 Interim Analysis

An interim analysis may be conducted after the last patient's Week 13 visit of the extension study or after the database of the ISIS 304801-CS6 and ISIS 304801-CS16 index studies are locked and unblinded. Both safety and efficacy information from this OLE study may be summarized during this interim analysis. Efficacy analyses will be detailed in the SAP.

10.6 Planned Methods of Analysis

All eCRF data, lab data transfers, as well as any outcomes derived from the data, will be provided in the patient data listings. Patient data listings will be presented for all patients enrolled into the study. Descriptive summary statistics including n, mean, median, standard deviation, standard error, interquartile range (25th percentile, 75th percentile), and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data by treatment group. Where appropriate, p-values

will be reported. All statistical tests will be conducted using 2-sided tests with 5% Type I error rates unless otherwise stated.

All efficacy endpoints will be assessed in the FAS and PPS. All safety assessments will be performed on the Safety Set. PK endpoints will be assessed in the PK Set as applicable.

10.6.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics by treatment group. The patient disposition will be summarized by treatment group of the index studies. All patients enrolled will be included in a summary of patient disposition.

10.6.2 Safety Analysis

Treatment duration and amount of Study Drug received will be summarized by treatment group of the index studies.

Patient incidence rates of AEs will be tabulated by MedDRA system organ class, MedDRA preferred term, and treatment group of the index studies. Narratives of treatment-emergent deaths, serious and significant AEs, including early withdrawals due to AEs, will also be provided.

All treatment-emergent AEs, all treatment-emergent AEs potentially related to Study Drug, all treatment-emergent serious AEs, and all treatment-emergent serious AEs potentially related to Study Drug will be summarized.

Injection Site Reactions (ISRs) will be summarized by treatment group of the index studies, MedDRA preferred term and severity.

Independently adjudicated events of MACE and pancreatitis will be summarized by treatment group of the index studies.

Laboratory tests to ensure patient safety including chemistry panel, complete blood count (CBC) with differential, coagulation panel, IM, complement etc., will be summarized by study visits by treatment group of the index studies.

These safety variables will also be presented as change and percent change from baseline over time after Study Drug administration, as appropriate.

Vital signs, weight, ECG measures, echocardiography assessments, and MRI assessments will be tabulated by treatment group of the index studies.

10.6.3 Efficacy Analysis

Percent change and change from baseline to Month 3, Month 6, and Month 12 in fasting TG will be summarized by treatment group of the index studies. Response rate of patients with fasting plasma TG < 750 mg/dL or achieving fasting TG $\geq 40\%$ reduction from baseline at Month 3, Month 6, and Month 12 will be summarized. Response analysis will also be conducted using a range of fasting plasma TG thresholds for determination of responder status.

Percent change and change from baseline to Month 3, Month 6, and Month 12 will also be summarized by treatment group of the index studies for other fasting lipid measures including non-HDL-C, apoB, HDL-C, apoA-1, VLDL-C, and LDL-C, total cholesterol, and fasting total apoC-III.

The incremental effects of volanesorsen on lipid measures will be explored and the association between changes in lipid parameters and total amount of drug received will be examined, as appropriate.

Frequency and severity of patient reported abdominal pain, adjudicated acute pancreatitis event rate, quality of life assessments, and comparison of other symptoms including eruptive xanthomas and lipemia retinalis will be summarized by treatment group of the index studies.

Additional details of the analyses to be conducted will be provided in the SAP.

10.6.4 Pharmacokinetic and Immunogenicity Analysis

10.6.4.1 Pharmacokinetic Analysis

For all patients, pre-dose and post-treatment volanesorsen plasma concentrations will be summarized using descriptive statistics, with stratification by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16 and IM status.

For patients in the PK subgroup only, non-compartmental PK analysis of volanesorsen will be carried out on each individual patient data set using data collected in the open label extension (OLE) study from the intensive PK subgroup, following a single dose (i.e., single-dose PK) or multiple doses (i.e., steady-state PK), depending on their earlier treatment in the index studies. On Week 1 Day 1 of the OLE study, patients who received placebo in the index study will receive the first treatment of volanesorsen (single-dose PK), while patients who received volanesorsen in the index studies had been on volanesorsen treatment for 12 months (ISIS 304801-CS6) or 6 months (ISIS 304801-CS16), thus the PK data collected from these patients reflect steady-state PK. The maximum observed drug concentration (C_{max}) and the time taken to reach C_{max} (T_{max}) will be obtained directly from the concentration-time data. Area under the plasma concentration-time curve from time zero to 24 hours ($AUC_{0\text{-}24hr}$) will be calculated using the linear trapezoidal rule. Apparent systemic (plasma) clearance after SC administration ($CL_{0\text{-}24hr}/F_{0\text{-}24hr}$) will be calculated from $CL_{0\text{-}24hr}/F_{0\text{-}24hr}$ = Actual Dose/$AUC_{0\text{-}24hr}$. Mean residence time (MRT) from time zero to 24 hours after the SC administration will be calculated from the equation, $MRT_{0\text{-}24hr} = AUMC_{0\text{-}24hr}/AUC_{0\text{-}24hr}$, where $AUMC_{0\text{-}24hr}$ is the area under the moment plasma concentration-time curve from time zero to 24 hours after the SC administration. Other PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist.

Plasma PK parameters will be summarized using descriptive statistics, with and without stratification by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16 and IM status. Additional details regarding the PK analysis will be described in the SAP.

Population PK, PK/PD, and covariate analysis may be performed if deemed appropriate, and results will be reported separately.

10.6.4.2 Immunogenicity Analysis

Immunogenicity (IM) results (screen positive/negative, confirmed positive/negative or not evaluable, and when applicable, titer of anti-volanesorsen antibodies) before, during, and after treatment with Study Drug (volanesorsen) (i.e., sample [anti-drug antibody] ADA status) will be listed by their prior treatment in study ISIS 304801-CS6 or ISIS 304801-CS16 and study day. Subject ADA status (positive/negative or not evaluable) for all evaluable patients, along with the study day associated with the first positive IM status emerged (T_{first}, i.e., onset of ADA development), the last positive IM status observed (T_{last}), the duration of ADA response (number of days between T_{first} and T_{last}) if appropriate, the last ADA sample collection day, and subject - peak titer if applicable, will be listed by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16 study day. Subjects with positive anti-volanesorsen antibody status may be further classified (when applicable) as being either 'persistent', 'transient', or 'not determinable', if deemed appropriate.

Additionally, the sample and subject IM incidence (number) and incidence rate (percent) will be summarized as the total number and percent of evaluated subjects with antibody negative, positive, and unknown status by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16. Furthermore, onset, duration, and titer of the ADA response, if applicable, will be summarized as median, quartiles (25% and 75%), and range.

Additional details regarding the IM data analysis will be described in the SAP.

Potential relationships between immunogenicity results (e.g., IM status) and selected efficacy (e.g., % change in fasting TG from baseline at 3-, 6-, and 12-month endpoints), safety, and PK (e.g., C_{trough}) measures will be evaluated using graphical analysis and statistical analysis. These analyses will be either conducted and included in the study report, or data pooled and analyzed from all available Phase 2 and 3 studies and reported separately.

11. INVESTIGATOR'S REGULATORY OBLIGATIONS

11.1 Informed Consent

The written informed consent document should be prepared in the language(s) of the potential patient population, based on an English version provided by the Sponsor.

Before a patient's participation in the trial, the Investigator is responsible for obtaining written informed consent from the patient after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific qualification procedures or any Study Drug are administered. The patient must be given sufficient time to consider whether to participate in the study.

The acquisition of informed consent and the patient's agreement or refusal to notify his/her primary care physician should be documented in the patient's medical records and the informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion (not necessarily an Investigator). The original signed informed consent form should be retained in the Study Master File and in any other locations required by institutional policy, and a copy of the signed consent form should be provided to the patient.

11.2 Ethical Conduct of the Study

The Guidelines of the World Medical Association (WMA) Declaration of Helsinki dated October 2002 the applicable regulations and guidelines of current Good Clinical Practice (GCP) as well as the demands of national drug and data protection laws and other applicable regulatory requirements will be strictly followed.

11.3 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent form, other written patient information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by the Sponsor before recruitment of patients into the study and shipment of volanesorsen. A copy of the written approval of any other items/materials that must be approved by the Study Center or IEC/IRB must also be received by the Sponsor before recruitment of patients into the study and shipment of Study Drug. The Investigator's Brochure must be submitted to the IEC/IRB for acknowledgement.

The Investigator must submit to and, where necessary, obtain approval from the IEC/IRB, for all subsequent protocol amendments and changes to the informed consent document. The Investigator should notify the IEC/IRB of deviations from the protocol in accordance with ICH GCP Section 4.5.2. The Investigator should also notify the IEC/IRB of serious adverse events occurring at the Study Center and other adverse event reports received from the Sponsor, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study. Copies of the Investigator's reports, all IEC/IRB submissions and the IEC/IRB continuance of approval must be sent to the Sponsor.

11.4 Patient Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained. On the case report forms (CRF) or other documents submitted to the Sponsor, patients should be identified by unique initials and a patient study number only. Documents that are not for submission to the Sponsor (e.g., signed informed consent forms) should be kept in strict confidence by the Investigator.

In compliance with Federal and local regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the patient to permit named representatives to have access to his/her study-related records without violating the confidentiality of the patient.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments

Protocol amendments must be made only with the prior approval of the Sponsor. Agreement from the Investigator must be obtained for all protocol amendments and amendments to the informed consent document. The regulatory authority and IEC/IRB must be informed of all amendments and give approval for any amendments likely to affect the safety of the patients or the conduct of the trial. The Investigator **must** send a copy of the approval letter from the IEC/IRB to the Sponsor.

12.2 Study Termination

The Sponsor reserves the right to terminate the study according to the terms of the site contract. The Investigator reserves the right to terminate their participation in the study, according to the terms of the site contract. The Investigator/Sponsor should notify the IEC/IRB in writing of the trial's completion or early termination and send a copy of the notification to the Sponsor.

12.3 Study Documentation and Storage

An electronic case report form (eCRF) utilizing an Electronic Data Capture (EDC) application will be used for this study.

The Investigator should ensure that all appropriately qualified persons to whom he/she has delegated trial duties are recorded on a Sponsor-approved Delegation of Site Responsibilities Form.

Source documents are original documents, data, and records from which the patient's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, imaging, and correspondence. In this study, CRFs may not be used as source documents.

The Investigator and Study Center staffs are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation in accordance with Section 8 of the ICH Guidelines (E6), suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Elements should include:

- Patient files containing completed CRFs, informed consents, and supporting copies of source documentation
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation and all correspondence to and from the IEC/IRB and the Sponsor
- If volanesorsen supplies are maintained at the Study Center, proof of receipt, volanesorsen Accountability Record, Return of volanesorsen for Destruction, final study volanesorsen reconciliation, and all volanesorsen-related correspondence

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

No study document should be destroyed without prior written agreement between the Sponsor or and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor.

12.4 Study Monitoring

The Sponsor representative and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the trial (e.g., CRFs and other pertinent data) provided that patient confidentiality is respected.

The Sponsor monitor is responsible for inspecting the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to patient medical records and other study-related records needed to verify the entries on the CRFs.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's Clinical Quality Assurance Department. Inspection of Study Center facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the trial conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

To ensure the quality of clinical data a clinical data management review will be performed on patient data received by the Sponsor. During this review, patient data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or Study Center notifications will be sent to the Study Center for completion and return to Sponsor.

The Principal Investigator will sign and date the indicated places on the CRF. These signatures will indicate that the principal Investigator inspected or reviewed the data on the CRF, the data queries, and the Study Center notifications, and agrees with the content.

12.5 Language

Case report forms must be completed in English. Generic names for concomitant medications should be recorded in English if possible, unless it is a combination drug, then record the trade name in English.

All written information and other material to be used by patients and investigative staff must use vocabulary and language that are clearly understood.

12.6 Compensation for Injury

The Sponsor maintains appropriate insurance coverage for clinical trials and will follow applicable local compensation laws. Patients will be treated and/or compensated for any study-related illness/injury in accordance with the information provided in the Compensation for Injury section of the Informed Consent document.

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14. APPENDICES

Appendix A Schedule of Procedures

Appendix A Schedule of Procedures

Study Period		Qual[a]	Treatment Period																					Post Treatment Follow-up	
Study Week		-2 to -1	Wk 1		Wk 4	Wk 8	Month 3		Wk 16	Wk 19	Wk 22	Month 6		Wk 29	Wk 32	Wk 35	Wk 38	Wk 41	Wk 44	Wk 47	Month 12		Wk 58	Wk 65
							Wk 12	Wk 13				Wk 25	Wk 26								Wk 51	Wk 52 or ET		
Study Day		-14 to -7	1	2	22	50	78	85	106	127	148	169	176	197	218	239	260	281	302	323	351	358	400	449
Visit Window+/- Days		0	0	0	2	2	2	2	3	3	3	2	2	3	3	3	3	3	3	3	2	2	7	7
Informed Consent		X																						
Outpatient Visit		X	X	X[k]	X[k]	X[k]	X[k]	X	X[k]	X[k]	X[k]	X[k]	X	X[k]	X[k]	X[k]	X	X[k]	X[k]	X[k]	X[k]	X	X[k]	X
Inclusion/Exclusion Criteria		X																						
Vital Signs + body weight (+ height on Day 1 only)		X	X		X	X		X					X				X					X		X
Physical Examination			X					X					X				X					X		X
12- lead ECG (triplicate)								X					X				X					X		X
MRI (liver/spleen)																						X[l]		
Echocardiography													X[l]									X[l]		
Blood Draw (Fasting)[c]	Chemistry Panel	X	X		X	X		X		X			X		X		X		X			X	X	X
	CBC with Differential[b]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Serum Lipid Panel	X	X		X	X	X	X				X	X				X				X	X		X
	Coagulation (aPTT, PT, INR)					X		X					X				X					X		
	hsCRP, HbA1c, FPG, and de-lipidated free glycerol		X					X					X									X		X
	Sedimentation Rate		X					X					X									X		X
	Complement (C5a, Bb)		X					X					X									X		X
	Plasma PK - Volanesorsen		X[m]	X	X	X		X					X				X					X		X
	Anti-Volanesorsen Antibodies		X		X	X		X					X				X					X		X
	FSH (women only, if applicable)																							
	Serum Pregnancy Test[d]	X			X	X		X		X			X		X		X		X			X	X	X
	Archived Serum & Plasma Samples[e]		X			X		X					X									X		X

Appendix A Schedule of Procedures *Continued*

Study Period	Qual[a]	Treatment Period																				Post Treatment Follow-up	
Study Week	-2 to -1	Wk 1		Wk 4	Wk 8	Month 3		Wk 16	Wk 19	Wk 22	Month 6		Wk 29	Wk 32	Wk 35	Wk 38	Wk 41	Wk 44	Wk 47	Month 12		Wk 58	Wk 65
						Wk 12	Wk 13				Wk 25	Wk 26								Wk 51	Wk 52 or ET		
Study Day	-14 to -7	1	2	22	50	78	85	106	127	148	169	176	197	218	239	260	281	302	323	351	358	400	449
Visit Window+/- Days	0	0	0	2	2	2	2	3	3	3	2	2	3	3	3	3	3	3	3	2	2	7	7
Urinalysis[c]	X	X[n]		X	X		X[n]		X[n]			X[n]		X[n]		X[n]		X[n]			X[n]	X[n]	X[n]
Fundus Photography[f]	X																				X[l]		
Genetic testing for FCS diagnosis (if not available in medical history)[g]	X																						
Postheparin Lipoprotein Lipase activity[h]	X																						
Weekly Study Drug: SC Injection		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Symptom Diary (weekly)	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Assessment(s)		X					X					X									X		X
Food/Drink Diary (quarterly)[i]		X					X					X									X		X
Diet/Alcohol Counseling[j]	X	X		X	X		X					X				X					X	X	X
Adverse Events	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a Qualification procedures performed (Please refer to Section 4.1)

b Each time a hematology lab is drawn and sent to the central laboratory for analysis an additional sample should be collected in parallel and analyzed locally. In the event that both the central and local sample are uninterpretable (e.g., due to hemolyzed or clumped blood samples) another sample must be repeated within 1-week

c Blood samples to be collected after an overnight fast of at least 10 hours and preferably not more than 12 hours. During treatment period urine and blood samples will be collected prior to Study Drug administration. Does not apply to 24-hour PK blood draw

d Females of childbearing potential only

e Serum and plasma samples will be collected and stored for follow-up exploration of laboratory findings and/or adverse events (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.) in this or subsequent clinical studies of volanesorsen

f If possible, fundus photography should be completed prior to administration of the first dose of Study Drug (ISIS 304801-CS16 rollover patients) and repeated at Week 52 (Please refer to Section 6.2.2.2)

Appendix A Schedule of Procedures Continued

Legend Text *Continued*

g Genetic testing can be conducted for study qualification (ISIS 304801-CS16 rollover patients); genetic testing will only be conducted if allowed in the geographic region and only after the patient has given specific written informed consent for genetic testing

h Post-heparin lipoprotein lipase activity can be conducted for study qualification (ISIS 304801-CS16 rollover patients; please refer to Section 6.2.10)

i In addition to diary, patients will be contacted at random times during the study to review their current eating and drinking habits

j To reinforce compliance to the diet and alcohol restrictions. Random diet/alcohol assessments (phone visits) will also be performed by dietician or study personnel

k Assessments and procedures to be conducted by either a home healthcare nurse, or the Study Center as arranged by the Study Center personnel

l A ± 7-day window is allowed for MRI, echocardiography procedures and fundus photography

m Full or abbreviated PK profile (see Appendix C)

n Expanded urinalysis (see Appendix B)

Appendix B List of Laboratory Analytes

Appendix B List of Laboratory Analytes

Based on emerging data from this or future studies, additional tests not listed below may be performed on stored samples to better characterize the profile of volanesorsen or other similar oligonucleotides.

Clinical Chemistry Panel

- Sodium
- Potassium
- Chloride
- Bicarbonate
- Total protein
- Albumin
- Calcium
- Magnesium
- Phosphorus
- Glucose
- BUN
- Creatinine
- Uric Acid
- Total bilirubin
- Direct (conjugated) bilirubin
- Indirect (unconjugated) bilirubin
- ALT
- AST
- Alkaline phosphatase

Coagulation

- aPTT (sec)
- PT (sec)
- INR

Lipid Panel

- Total Cholesterol
- LDL-C
- HDL-C
- Triglycerides
- Non-HDL-C
- VLDL-C
- apoA-1
- apoB
- apoC-III

Hematology

- Red blood cells
- Hemoglobin
- Hematocrit
- MCV, MCH, MCHC
- Platelets
- White blood cells
- WBC Differential (% and absolute)
  - Neutrophils
  - Eosinophils
  - Basophils
  - Lymphocytes
  - Monocytes

Pharmacokinetics[1] & Immunogenicity

- Volanesorsen levels in plasma
- Anti-volanesorsen antibodies in plasma

Other assessments

- hsCRP
- Sedimentation Rate
- C5a, Bb
- De-lipidated free glycerol
- HbA1c, FPG

Urinalysis

- Color
- Appearance
- Specific gravity
- pH
- Protein
- Blood
- Ketones
- Urobilinogen
- Glucose
- Bilirubin
- Leukocyte esterase
- Nitrate
- Microscopic examination[2]

Additional Measures for Expanded Urinalysis

- Total protein (quantitative)
- Microalbumin
- β2-microglobulin

1 Plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, IM testing (or possibly for purposes of IM assay development and/or validation), or to assess other actions of volanesorsen with plasma constituents

2 Will be performed on abnormal findings unless otherwise specified

Appendix C Pharmacokinetic Sampling Schedule

Appendix C Pharmacokinetic Sampling Schedule

Blood samples for the determination of plasma volanesorsen concentrations will be collected prior to dosing, and at various times throughout the dosing and post-treatment follow-up period as noted in the tables below.

PK Sampling Schedule (All Patients except PK Subgroup)

Week	**Wk 1**	**Wk 4**	**Wk 8**	**Wk 13**	**Wk 26**	**Wk 38**	**Wk 52**	**Wk 65**
Study Day	**D1**	**D22**	**D50**	**D85**	**D176**	**D260**	**D358**	**D449**
Visit Window +/- Days	0	2	2	2	2	3	2	7
Time Point	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime

PK Sampling Schedule (PK Subgroup only*)

Week	**Wk 1**	**Wk 1**	**Wk 4**	**Wk 8**	**Wk 13**	**Wk 26**	**Wk 38**	**Wk 52**	**Wk 65**
Study Day	**D1**	**D2**	**D22**	**D50**	**D85**	**D176**	**D260**	**D358**	**D449**
Visit Window +/- Days	0	0	2	2	2	2	3	2	7
Time Point	Pre-dose, 1, 2, 3, 4, 6, 8, and 12 hrs post-dose	24 hrs post-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime

* Patients at selected sites will be asked to participate in the extended 24-hour PK profile beginning on Study Day 1. Participation is optional.

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

The following grading recommendations for adverse events relating to lab test abnormalities are based upon the **Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010**

Adverse Event	Mild	Moderate	Severe
Hematology			
aPTT prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage
Eosinophils increased†	650 – 1,500 cell/mm^3	1,501 - 5,000 cell/mm^3	>5,000 cell/mm^3
Fibrinogen decreased	<1.0 - 0.75 x LLN or <25% decrease from baseline	<0.75 - 0.5 x LLN or 25 - <50% decrease from baseline	<0.5 x LLN or ≥50% decrease from baseline
Hemoglobin decreased (Anemia)	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated
Hemoglobin increased	Increase in >0 - 2 g/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 g/dL above ULN or above baseline if baseline is above ULN	Increase in >4 g/dL above ULN or above baseline if baseline is above ULN
INR increased	>1 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation
Lymphocyte count decreased	<LLN - 800/mm^3; <LLN - 0.8 x 10^9/L	<800 - 500/mm^3; <0.8 - 0.5 x 10^9 /L	<500 /mm^3; <0.5 x 10^9 /L
Lymphocyte count increased	-	>4000/mm^3 - 20,000/mm^3	>20,000/mm^3
Neutrophil count decreased	<LLN - 1500/mm^3; <LLN - 1.5 x 10^9 /L	<1500 - 1000/mm^3; <1.5 - 1.0 x 10^9 /L	<1000/mm^3; <1.0 x 10^9 /L
Platelet count decreased	<LLN - 75,000/mm^3; <LLN - 75.0 x 10^9 /L	<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9 /L	<50,000/mm^3; <50.0 x 10^9 /L
White blood cell decreased	<LLN - 3000/mm^3; <LLN - 3.0 x 10^9 /L	<3000 - 2000/mm^3; <3.0 - 2.0 x 10^9 /L	<2000/mm^3; <2.0 x 10^9 /L
Chemistry			
Acidosis	pH <normal, but >=7.3	-	pH <7.3
Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Alkalosis	pH >normal, but ≤7.5	-	pH >7.5
Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 x ULN
Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

Adverse Event	Mild	Moderate	Severe
Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer
CD4 lymphocytes decreased	<LLN - 500/mm^3; <LLN - 0.5 x 10^9 /L	<500 - 200/mm^3; <0.5 - 0.2 x 10^9 /L	<200/mm^3; <0.2 x 10^9 /L
CPK increased*	>ULN - <6 ULN	6 - 10 x ULN	>10 x ULN
Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 x ULN
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 mg/dL; >3.1 mmol/L; Ionized calcium >1.6 mmol/L; hospitalization indicated
Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 mg/dL; >13.9 mmol/L; hospitalization indicated
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0; hospitalization indicated
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 mg/dL; >1.23 mmol/L
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 mmol/L; hospitalization indicated
Hyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 mg/dL; <1.75 mmol/L; Ionized calcium <0.9 mmol/L; hospitalization indicated
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 mg/dL; <3.0 mmol/L	<40 mg/dL (<2.2 mmol/L) AND requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions‡
Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 mmol/L; hospitalization indicated
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 mg/dL; <0.4 mmol/L
Hyponatremia	<LLN - 130 mmol/L	-	<130 mmol/L
Hypophosphatemia	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 mg/dL; <0.6 mmol/L
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

Adverse Event	Mild	Moderate	Severe
Urine			
Proteinuria Adults Children	1+ proteinuria; urinary protein <1.0 g/24 hrs -	2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs; Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Urinary protein ≥3.5 g/24 hrs; Urine P/C >1.9
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated

†Grading for this parameter is derived from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007

*Grading for this parameter is derived from the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0, Nov 2014

‡Modified for consistency with the ADA and Endocrine Society Guidelines (Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. Diabetes Care 2013;36:1384-95)

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ISIS 304801-CS7

The APPROACH Open Label Extension Study

Volanesorsen (ISIS 304801)

An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol Supplement 1 - UK – 15 April 2016

EudraCT No: 2015-003755-21

ISIS 304801-CS7

The APPROACH Open Label Extension Study

Volanesorsen (ISIS 304801)

An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol Supplement 1 - UK – 15 April 2016

Sponsor:

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Protocol Supplement Signature Page

Protocol Number:	ISIS 304801-CS7
Protocol Title:	An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Supplement:	1 - UK
Date:	15 April 2016

I hereby acknowledge that I have read and understand the attached clinical protocol supplement for the protocol entitled "An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)", dated 15 April 2016, and agree to conduct the study as described herein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice (E6).

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc.

_____

Investigator's Signature

_____ _____

Investigator's Name *(please print)* Date (DD Month YYYY)

PROTOCOL SUPPLEMENT - UK

Protocol Number: ISIS 304801-CS7

Protocol Title: An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Supplement: 1 - UK

Date: 15 April 2016

The purpose of this supplement (to the global study protocol) is to fulfill MHRA requirements.

The following changes will be made to the protocol:

1. To indicate that the DSMB is independent.
2. To revise the contraceptive requirements to state that abstinence is only acceptable as true abstinence, i.e., when it is in line with the preferred and usual lifestyle of the patient.
3. To increase the frequency of the pregnancy testing.
4. To clarify guidance on determining relatedness of a SUSAR.

The following table provides a summary list of the modifications to the protocol.

LIST OF PROTOCOL MODIFICATIONS

Section	Modification	Rationale
Section 3.6 Data and Safety Monitoring Board	**Was:** The Data and Safety Monitoring Board (DSMB) will review (as needed) safety, tolerability and efficacy data collected on volanesorsen during this study. Based on its ongoing assessment of the safety and tolerability of volanesorsen, the DSMB will provide recommendations to the Sponsor for modifying, stopping or continuing the study as planned. Details on the safety assessments, frequency of review and meeting schedules are outlined in the DSMB Charter and/or the statistical analysis plan (SAP). **Is:** An **independent** Data and Safety Monitoring Board (DSMB) will be assembled to review safety, tolerability and efficacy (as needed) data collected on ISIS 304801 during this study. Based on its ongoing assessment of the safety and tolerability of ISIS 304801, the DSMB will provide recommendations to the Sponsor for modifying, stopping or continuing the study as planned. Details on the safety assessments, frequency of review, meeting schedules and controlled access to unblinded data are outlined in the DSMB Charter and/or the statistical analysis plan (SAP).	To clarify that the DSMB is independent
Section 5.1 Inclusion Criteria Section 6.3.1 Contraception Requirements	**New:** * Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception	Per the MHRA's guidance to state that only true abstinence would be acceptable, and that periodic abstinence is not an acceptable method of contraception
Appendix A Schedule of Procedures	Pregnancy testing added at Weeks 4, 19, 32, 44, and 58 (See Appendix A below)	To reduce the time period between pregnancy tests
Section 9.2 Regulatory Requirements	**Was:** The Sponsor or designee will evaluate the available information and decide if there is a reasonable possibility that volanesorsen caused the AE and, therefore, meets the definition of a SUSAR. **Is:** In addition to the Investigator's assessment of relatedness, the Sponsor or designee will evaluate the available information and perform an independent assessment of relatedness. While the Sponsor may upgrade an investigator's decision it is not permissible to downgrade the investigator's opinion for the purposes of determining whether the SAE meets the definition of a SUSAR.	To clarify guidance on determining relatedness of a SUSAR

Appendix A Schedule of Procedures

Study Period		Qual[a]	Treatment Period														Post Treatment Follow-up	
Study Week		-2 to -1	Wk 1		Wk 4	Wk 8	Month 3		Wk 19	Month 6		Wk 32	Wk 38	Wk 44	Month 12		Wk 58	Wk 65
							Wk 12	Wk 13		Wk 25	Wk 26				Wk 51	Wk 52 or ET		
Study Day		-14 to -7	1	2	22	50	78	85	127	169	176	218	260	302	351	358	400	449
Visit Window+/- Days		0	0	0	2	2	2	2	3	2	2	3	3	3	2	2	7	7
Informed Consent		X																
Outpatient Visit		X	X	X	X	X	X[h]	X	X[h]	X[h]	X	X[h]	X	X[h]	X[h]	X	X[h]	X
Inclusion/Exclusion Criteria		X																
Vital Signs + body weight (+ height on Day 1 only)		X	X		X	X		X			X		X			X		X
Physical Examination			X					X			X		X			X		X
12- lead ECG (triplicate)								X			X		X			X		X
MRI (liver/spleen)																X[i]		
Echocardiography											X[i]					X[i]		
Fundus Photography[b]		X														X[i]		
Blood Draw (Fasting)[c]	Chemistry Panel	X	X		X	X		X	X[h]		X	X[h]	X	X[h]		X	X[h]	X
	CBC with Differential	X	X		X	X		X	X[h]		X	X[h]	X	X[h]		X	X[h]	X
	Serum Lipid Panel	X	X		X	X	X[h]	X		X[h]	X		X		X[h]	X		X
	Coagulation (aPTT, PT, INR)					X		X			X		X			X		
	hsCRP, HbA1c, FPG, and de-lipidated free glycerol		X					X			X					X		X
	Sedimentation Rate		X					X			X					X		X
	Complement (C5a, Bb)		X					X			X					X		X
	Plasma PK - Volanesorsen		X[k]	X	X	X		X			X		X			X		X
	Anti-Volanesorsen Antibodies		X		X	X		X			X		X			X		X
	FSH (women only, if applicable)																	
	Serum Pregnancy Test[d]	X			X	X		X	X		X	X	X	X		X	X	X
	Archived Serum & Plasma Samples[e]		X			X		X			X					X		X

Appendix A Schedule of Procedures *Continued*

Study Period	Qual[a]	Treatment Period														Post Treatment Follow-up	
Study Week	-2 to -1	Wk 1		Wk 4	Wk 8	Month 3		Wk 19	Month 6		Wk 32	Wk 38	Wk 44	Month 12		Wk 58	Wk 65
						Wk 12	Wk 13		Wk 25	Wk 26				Wk 51	Wk 52 or ET		
Study Day	-14 to -7	1	2	22	50	78	85	127	169	176	218	260	302	351	358	400	449
Visit Window+/- Days	0	0	0	2	2	2	2	3	2	2	3	3	3	2	2	7	7
Urinalysis[c]	X	X[j]		X	X		X[j]	X[j,h]		X[j]	X[j,h]	X[j]	X[j,h]		X[j]	X[j,h]	X[j]
Weekly Study Drug: SC Injection		X		X	X	X	X	X	X	X	X	X	X	X	X		
Symptom Diary (weekly)	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Assessment(s)		X					X			X					X		X
Food/Drink Diary (quarterly)[f]		X					X			X					X		X
Diet/Alcohol Counseling[g]	X	X		X	X		X			X		X			X	X	X
Adverse Events	X	X		X	X		X			X		X			X		X
Concomitant Medication	X	X		X	X		X			X		X			X		X

a Qualification procedures performed (Please refer to Section 4.1)

b If possible, prior to administration of the first dose of Study Drug and repeated at Week 52 (Please refer to Section 6.2.2.2)

c Blood samples to be collected after an overnight fast of at least 10 hours. During treatment period urine and blood samples will be collected prior to Study Drug administration. Does not apply to 24-hour PK blood draw

d Females of childbearing potential only

e Serum and plasma samples will be collected and stored for follow-up exploration of laboratory findings and/or adverse events (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.) in this or subsequent clinical studies of volanesorsen

f In addition to diary, patients will be contacted at random times during the study to review their current eating and drinking habits

g To reinforce compliance to the diet and alcohol restrictions. Random diet/alcohol assessments (phone visits) will also be performed by dietician or study personnel

h To be collected by either a clinical service, or Study Center as arranged by the Study Center personnel. Approval for study procedures to be conducted by a clinical service on other outpatient visit days will require prior approval by the Sponsor.

i A ± 7 day window is allowed for MRI, echocardiography procedures and fundus photography

j Expanded urinalysis (see Appendix B)

k Full or abbreviated PK profile (see Appendix C)

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ISIS 304801-CS7

The APPROACH Open Label Extension Study

Volanesorsen (ISIS 304801)

An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol Amendment 1 –2 February 2016

EudraCT No: 2015-003755-21

ISIS 304801-CS7

The APPROACH Open Label Extension Study

Volanesorsen (ISIS 304801)

An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Protocol Amendment 1 – 2 February 2016

Protocol History:

Original Protocol: 28 August 2015

Sponsor:

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Ionis Protocol Number: ISIS 304801-CS7

Protocol Amendment 1

EudraCT No: 2015-003755-21

Clinical Phase: 3

The APPROACH Open Label Extension Study

Volanesorsen (ISIS 304801)

An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

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Collaborator: Akcea Therapeutics
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Cambridge, MA 02142

Date: 2 February 2016

Confidentiality Statement

This document contains confidential information of Ionis Pharmaceuticals, Inc., that must not be disclosed to anyone other than the recipient study staff and members of the independent ethics committee, institutional review board, or authorized regulatory agencies. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc.

Protocol Signature Page

Protocol Number: ISIS 304801-CS7

Protocol Title: An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Amendment: Amendment 1

Date: 2 February 2016

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)", dated 2 February 2016, and agree to conduct the study as described herein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice (E6).

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc.

Investigator's Signature

Investigator's Name *(please print)*

Date (DD Month YYYY)

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PROTOCOL AMENDMENT

Protocol Number:	ISIS 304801-CS7
Protocol Title:	An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Amendment Number:	1
Amendment Date:	2 February 2016

The purpose of this protocol amendment is to implement the following modifications to Protocol ISIS 304801-CS7 dated 28 August 2015:

1. To update the approximate anticipated number of patients that may enroll into the study (now approximately 70 patients) so that the number of patients is reflective of the estimated number of qualified patients from the ISIS 304801-CS6 and ISIS 304801-CS16 index studies.
2. To define the specific patient population from ISIS 304801-CS16 who will be allowed to enter the Open Label Extension Study.
3. Clarification of when final assessments from the ISIS 304801-CS6 and ISIS 304801-CS16 index studies may be used for enrollment into ISIS 304801-CS7.
4. Clarification of how food and alcohol will be monitored during the study.
5. An addition to the platelet monitoring rule language to allow for more frequent monitoring has been included.
6. To provide guidance to Investigators with enrolled FCS patients who also have T2DM. Specific glucose monitoring rules are provided for patients on insulin and oral antidiabetic medications. The definition of documented severe hypoglycemia is included and safety monitoring rules have been defined. Also, specific monitoring rules are incorporated into the protocol for hyperglycemic events.

Minor administrative changes or corrections (not included in the list of changes below) have been made throughout the protocol in order to improve the overall clarity of the protocol but these changes do not impact the study design.

The following table provides a summary list of changes to the protocol:

Protocol Section	Description of Change	Rationale
Synopsis Section 3: Experimental Plan Section 10.2: Sample Size	Up to approximately 50 patients dosed has been changed to up to approximately 70 patients dosed.	Reflective of the updated patient numbers in the ISIS 304801-CS6 study and the addition of ISIS 304801-CS16 patients - with a diagnosis of FCS who will be allowed to enter the Extension Study after successful completion of ISIS 304801-CS16.
Synopsis Study Population: Inclusion Criteria #3 Section 5.1: Inclusion Criteria #3	3. Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement. Patients who are enrolled in ISIS 304801-CS16 must also meet the following criteria in order to enter into the Extension Study: a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L) b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) by documentation of at least one (1) of the following: • Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoCII, GPIHBP1, or LMF1) • Post heparin plasma LPL activity of ≤ 20% of normal c. Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 study	Inclusion of the specific criteria that must be met in order for patients who successfully complete ISIS 304801-CS16 to enter into the Open Label Extension Study.
Section 4.1: Qualification	Eligibility requirements provided for enrollment into the extension study.	Clarification of when final assessments from the ISIS 304801-CS6 or ISIS 304801-CS16 study may be used for qualification.
Section 6.1.1 Qualification Appendix A	Please refer to Section 4.1 and Appendix A.	Deletion of repetitive information in Section 6.1.1 of when final assessments from ISIS 304801-CS6 or ISIS 304801-CS16 can be used for qualification. Qualification assessments explained in Section 4.1
Section 6.1.2 Study Procedures	Approval for study procedures to be conducted by a clinical service on other outpatient visit days will require prior approval by the Sponsor.	Blood sampling for lipid panels at Weeks 12, 25, and 51 may be conducted by a clinical service if more convenient for the patient. Patient must get prior approval from the Sponsor for study procedures to be conducted by a clinical service on days not listed above

Protocol Section	Description of Change	Rationale
Section 6.2.2.1 Eruptive Xanthoma Section 6.2.2.2 Lipemia Retinalis Section 10.1.1 Efficacy Endpoints	Inquiries into the number and duration of Eruptive Xanthoma by study staff will occur at each clinic visit. Fundus photography will be performed prior to Day 1 Study Drug administration and at Week 52	Eruptive Xanthoma and Lipemia Retinalis included as efficacy endpoints to obtain additional clinical endpoint data.
Section 6.2.8: Diet Monitoring	Explanation of how food/alcohol will be monitored throughout the course of the study.	Clarification of how and when food/alcohol will be monitored by the patient, dietician or qualified study personnel.
Section 8.5.2: Safety Monitoring Rules for Platelet Count Results	Addition to platelet monitoring rules that more frequent testing may be required.	More frequent monitoring of platelets may be warranted if a patient is experiencing a significant decline in platelet count.
Section 8.5.6 Section 8.5.7 Section 8.5.8 Glucose Monitoring in T2DM	Addition of monitoring rules for patients with T2DM. Monitoring rules established for patients on insulin and oral antidiabetic medications. Also included are monitoring rules for documented hypoglycemia and hyperglycemia.	Added sections to enhance safety monitoring for 52-week study in diabetic patients with FCS.
Appendix A Footnote “j”	A ±7 day window is allowed for MRI and echocardiography	Window expanded from 2 days to 7 days for scheduling flexibility and patient convenience.

PROTOCOL SYNOPSIS

Protocol Title	An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Study Phase	3
Indication	Familial Chylomicronemia Syndrome
Study Objectives	To evaluate the safety and efficacy of extended dosing with volanesorsen (volanesorsen sodium 300 mg) in patients with FCS
Study Design	This is a multi-center, open-label extension study of ISIS 304801-CS6 and ISIS 304801-CS16. All patients will receive volanesorsen 300 mg once per week for 52 weeks. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period. Following the Week 52 visit, patients will enter a 13 week post-treatment evaluation period.
Number of Patients	Up to approximately 70 patients dosed
Study Population	Inclusion Criteria: 1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law 2. Age ≥ 18 years at time of informed consent 3. Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement. Patients who are enrolled in ISIS 304801-CS16 must also meet the following criteria in order to enter into the Extension Study: a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L) b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) by documentation of at least one (1) of the following: • Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoCII, GPIHBP1, or LMF1) • Post heparin plasma LPL activity of ≤ 20% of normal c. Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 study 4. Able and willing to participate in a 65-week study 5. Satisfy one (1) of the following: a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved), abstinent, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration

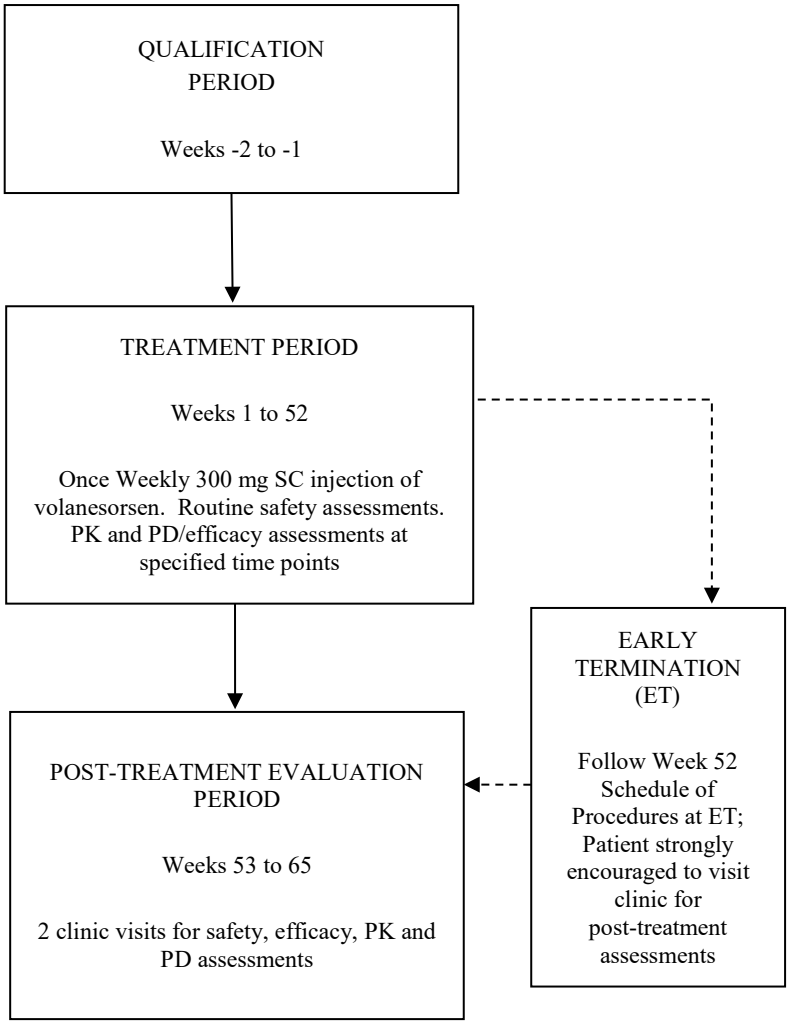
PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	Inclusion Criteria: *Continued* b. Males: Surgically sterile, abstinent or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration Exclusion Criteria: • Have any new condition or worsening of existing condition which in the opinion of the Investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study Unwilling to comply with lifestyle requirements for the duration of the study (Section 6.3)
Treatment Group	Volanesorsen 300 mg once per week
Study Drug Administration	Volanesorsen will be administered as subcutaneous (SC) injections.
Dose Adjustments	Dose adjustments, including dose interruptions and/or decreasing the dose frequency will be allowed for safety or tolerability after consultation with the Sponsor Medical Monitor.
Rationale for Dose and Schedule Selection	The dose of 300 mg once weekly was chosen for the double-blinded placebo-controlled Phase 3 index studies (ISIS 304801-CS6- and ISIS 304801-CS16) based on the pharmacodynamic and safety analysis of the Phase 2 studies which included a subset of patients with FCS. This is an extension to the ISIS 304801-CS6 and ISIS 304801-CS16 index studies. Only the subset of patients from ISIS 304801-CS16 with FCS diagnosis may enter the Extension Study. (Please refer to inclusion criteria #3, above)
Study Visit Schedule and Procedures	The study for an individual patient will generally consist of the following periods: • A qualification period of up to 2 weeks (unless approved by the Sponsor). Please refer to Section 4.1 and Appendix A. A 52-week treatment period during which volanesorsen will be administered as a once weekly SC injection • A 13-week post-treatment evaluation period The patients, Investigators, study staff, and the Sponsor will remain blinded to lipid data through the last patient's Week 13 visit of the extension study or until results from the database locks for the ISIS 304801-CS6 and ISIS 304801-CS16 index studies becomes available, whichever comes first. Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), adverse events (AE), concomitant medication/procedure information, lipid panel, volanesorsen plasma concentrations, immunogenicity (IM) testing, liver/spleen magnetic resonance imaging (MRI), ECGs, echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Dietary counseling will be repeated at intervals throughout the treatment and follow-up period and a daily food/drink diary will be completed for the week prior to each quarterly visit by each patient. Following the Week 52 visit, patients will enter the 13-week post-treatment evaluation period.

PROTOCOL SYNOPSIS *Continued*

Safety and Tolerability Evaluations	Overall safety and tolerability of volanesorsen will be assessed by determining the incidence and severity of adverse and serious adverse events (including independently adjudicated events of acute pancreatitis and MACE), withdrawals due to adverse events, and changes in laboratory and other safety parameters.
Planned Analyses	Safety Endpoints: • Adverse events including adjudicated events of acute pancreatitis and MACE • Vital signs and weight • Physical examinations • Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis) • Echocardiography • Electrocardiograms (ECGs) • Use of concomitant medications • MRIs Efficacy Endpoints: • Percent change and absolute change from baseline in fasting TG • Frequency and severity of patient reported abdominal pain during the treatment period • Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-high-density lipoprotein-cholesterol (non-HDL-C), apolipoprotein B [apoB], high-density lipoprotein-cholesterol (HDL-C), apolipoprotein A-1 [apoA-1], very-low-density lipoprotein-cholesterol (VLDL-C), and LDL-C • Percent change from baseline in fasting total apolipoprotein C-III (apoC-III) • Quality of Life questionnaires (EQ-5D, SF-36) • Adjudicated acute pancreatitis event rate • Other symptoms: eruptive xanthoma, lipemia retinalis
Pharmacokinetic Evaluations	Plasma samples will be taken from all patients for the measurement of volanesorsen as follows: trough levels (pre-dose) throughout treatment and post-treatment levels during the post-treatment follow-up period. In a subset of patients, more frequent assessment of plasma concentrations of volanesorsen will be performed to determine volanesorsen pharmacokinetic parameters. Plasma sample collection time points are detailed in Appendix A and Appendix C.
Statistical Considerations	No sample size calculations were performed as this is an extension study to the double-blind placebo controlled ISIS 304801-CS6 and ISIS 304801-CS16 index studies.
Sponsor	Ionis Pharmaceuticals, Inc.
Collaborator	Akcea Therapeutics

STUDY DESIGN AND TREATMENT SCHEMA



STUDY GLOSSARY

Abbreviation/Acronym	Definition
ADA	anti-drug antibody
AE	adverse Event
ALP	alkaline Phosphatase
ALT	alanine Aminotransferase
ANA	antinuclear Antibody
apoA-1	apolipoprotein A-1
apoB	apolipoprotein B
apoC-III	apolipoprotein C-III
apoE	apolipoprotein E
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
CBC	complete blood count
C_{max}	maximum observed drug concentration
CRF	case report form
DNA	deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
ET	early termination
FAS	full analysis set
FCS	Familial Chylomicronemia Syndrome
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
GPIHBP1	Glycosylphosphatidylinositol-anchored HDL-binding Protein 1
HAPI	Heritability and Phenotype Intervention
HbA1c	Glycated Hemoglobin
HDL	High-Density Lipoprotein
HDL-C	High-Density Lipoprotein-Cholesterol
hsCRP	High-sensitivity C-reactive protein
ICH	International Conference on Harmonization
IDL	Intermediate density lipoprotein
IEC	Independent Ethics Committee
IM	immunogenicity
Index Studies	ISIS 304801-CS6 and ISIS 304801-CS16

INR	International Normalized Ratio
IRB	Institutional Review Board
IXRS	Interactive Voice/Web-Response System
LDL	Low-Density Lipoprotein
LDL-C	Low-Density Lipoprotein-Cholesterol
LMF1	Lipase Maturation Factor 1
LPL	Lipoprotein Lipase
MACE	Major Acute Cardiovascular Event
MOE	2′-*O*-(2-methoxyethyl)
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NCS	not clinically-significant
NOAEL	No-Observed-Adverse-Effect Level
non-HDL-C	Non-High-Density Lipoprotein-Cholesterol
OLE	Open Label Extension
OTC	over the counter
PFS	prefilled syringe
PD	pharmacodynamic
PK	pharmacokinetic
PPS	per protocol set
PT	prothrombin time
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SUSAR	suspected unexpected serious adverse reaction
T2DM	type 2 diabetes mellitus
T_{max}	time to maximal concentration
TG	triglycerides
Treatment-emergent	occurring after first dose of Study Drug
TRL	Triglyceride-Rich Lipoproteins
ULN	upper limit of normal
VLDL	Very-Low-Density Lipoprotein
VLDL-C	Very-Low-Density Lipoprotein-Cholesterol
VLDL-TG	Lipoprotein-Triglyceride
WMA	World Medical Association

1. OBJECTIVES

The objective of the study is to evaluate the safety and efficacy of extended dosing with volanesorsen in patients with familial chylomicronemia syndrome.

2. BACKGROUND AND RATIONALE

2.1 Overview of Disease

Familial Chylomicronemia Syndrome (FCS) is an inherited disease characterized by severe hypertriglyceridemia and chylomicronemia, and risk or history of pancreatitis. It is a rare autosomal recessive disease that can be diagnosed either in childhood or adulthood.

Fasting plasma triglyceride (TG) levels in FCS patients are typically 10-fold to 100-fold above normal (1,500 to 15,000 mg/dL), despite extreme dietary fat restriction (20 g or approximately 15-20% of daily calorie intake) (Brunzell 1999-2011). Patients with FCS often present in infancy or childhood with frequent and severe abdominal pain, repetitive colicky pain, repeated episodes of potentially fatal acute pancreatitis, and failure to thrive (Brunzell 1999-2011; Tremblay et al. 2011). Physical examination frequently reveals eruptive xanthomas, lipemia retinalis and hepatosplenomegaly, and plasma from patients appears lactescent, interfering with determination of other laboratory parameters (Tremblay et al. 2011).

Patients with fasting triglyceride levels > 10 mmol/L probably have a component of chylomicronemia. Clinical diagnosis would include evidence of clinical features of chylomicronemia syndrome and secondary causes such as uncontrolled type 1 or type 2 diabetes mellitus (T2DM), hypothyroidism, poor diet, alcohol use, nephrotic syndrome or use of associated medications should be ruled out. The diagnosis of FCS may be made more specifically by genotyping or confirmation of very low or absent lipoprotein lipase (LPL) enzyme activity in post heparin plasma (Brunzell 1999-2011).

Patients with FCS carry a heavy burden of medical complications, the most serious, as described above, being an extreme risk of recurrent and potentially fatal pancreatitis. Due to the recurrent episodes of acute pancreatitis, these patients may also develop chronic pancreatitis and signs of exocrine or endocrine pancreatic insufficiency, including diabetes mellitus (Gaudet et al. 2013). While the pathophysiology underlying chylomicron-related pancreatitis has not been completely elucidated, one (1) hypothesis is that large chylomicrons lodged in pancreatic capillaries are exposed to pancreatic lipase, with the subsequent release of free fatty acids through the hydrolysis of chylomicron-associated TGs. High concentrations of free fatty acids are thought to damage pancreatic cells leading to emergent pancreatitis (Yang et al. 2009; Berglund et al. 2012).

The etiology of extreme hypertriglyceridemia in FCS is considered to be ineffective triglyceride clearance, due to an extremely low level of LPL activity. LPL normally functions to hydrolyze triglycerides (TG) in chylomicrons along the luminal surface of capillaries, mainly in heart, skeletal muscle, and adipose tissue, promoting triglyceride clearance from the circulation. LPL is regulated by a number of key genes, and loss-of-function mutations in one of these genes, or the LPL gene itself, results in FCS (Surendran et al. 2012). In addition to loss of function mutations, null mutations, and nonsense mutations in the LPL gene, other genes currently identified in FCS patients, and known to directly influence LPL activity include:

apolipoprotein C-II (APOC2) a cofactor for LPL (Schuster et al. 2011); apolipoprotein A-V (APOA5) an enhancer of LPL activity (Schaap et al. 2004); lipase maturation Factor 1 (LMF1), a transmembrane protein involved in LPL maturation (Doolittle et al. 2009); glycosylphosphatidylinositol-anchored HDL-binding protein 1 (GPIHBP1), a capillary endothelial cell protein that provides a platform for LPL-mediated processing of chylomicrons (Beigneux et al. 2007).

2.2 Therapeutic Rationale

Apolipoprotein C-III (ApoC-III), a key regulator of plasma triglyceride levels, is a 79 amino acid glycoprotein synthesized principally in the liver (Ooi et al. 2008; Figure 1). ApoC-III is a major regulator of lipoprotein metabolism and plays a pivotal role in regulating plasma TG levels (Chan et al. 2008). It is a component of triglyceride-rich lipoproteins (TRLs) and a potent inhibitor of LPL (Lemieux et al. 2003). At higher concentrations apoC-III also inhibits hepatic lipase activity (Kinnunen and Ehnolm 1976), an enzyme which plays an important role in the conversion of dense very-low-density lipoprotein (VLDL) to intermediate density lipoprotein (IDL) and to LDL (Mendivil et al. 2010), as well as in the remodeling of HDL (Brown et al. 2010). In addition, increased apoC-III content adversely affects apoE-mediated hepatic uptake of TG-rich remnants (Mann et al. 1997). Thus, elevated plasma apoC-III levels are associated with impaired hydrolysis and retarded clearance of TG-rich particles, resulting in the accumulation of lipoprotein-triglyceride (VLDL-TG) and chylomicrons in plasma and the development of hypertriglyceridemia (Ito et al. 1990).

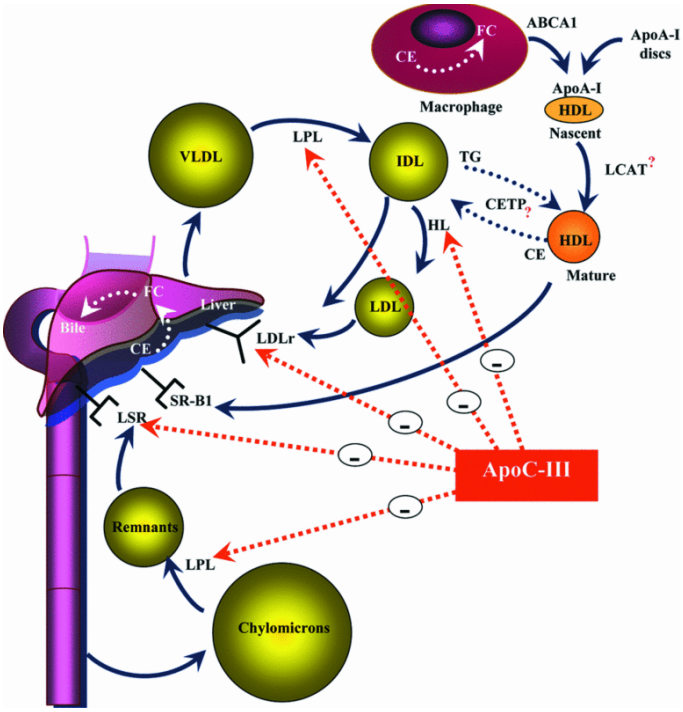


Figure 1 ApoC-III Regulates Lipoprotein Metabolism by Multiple Mechanisms

From Ooi et al. 2008; ABCA1 = ATP-binding cassette A1, apo = apolipoprotein, CE = cholesterol ester, CETP = cholesterol ester transfer protein, FC = free cholesterol, HDL = high-density lipoprotein, HL = hepatic lipase, IDL = intermediate-density lipoprotein, LCAT = lecithin cholesterol acyltransferase, LDL = low-density lipoprotein, LDLr = LDL receptor, LPL = lipoprotein lipase, LSR = lipolysis-stimulated receptor, SR-B1 = scavenger receptor B-1, TG = triglyceride, VLDL = very low-density lipoprotein.

Mechanistically, FCS is primarily a consequence of ineffective clearance of TRL. ApoC-III is a prominent component of TRL (e.g., VLDL and chylomicrons). In addition to its role in inhibiting LPL, apoC-III inhibits TRL remnant (TG-depleted remnant lipoprotein) uptake by hepatic lipoprotein receptors by steric inhibition of the interaction of apoE with these receptors.

Human genetic data have demonstrated positive phenotypic associations with loss (e.g., null or nonsense mutations) and negative effects with gain of function mutations (Atzmon et al. 2006; Pollin et al. 2008; Petersen et al. 2010). A novel nonsense mutation in the apoC-III gene was identified in the heritability and phenotype intervention (HAPI) heart study in Old Order Amish that results in lower plasma apoC-III and TG levels and lower LDL-C, increased HDL-C and reduced atherosclerosis (Pollin et al. 2008). In another study involving a group of 214 Ashkenazi Jews of advanced age (had passed or nearly reached 100 years of age), genotype analysis revealed a polymorphism in the apoC-III gene (APOC3-641CC genotype) with a clear pattern of age-dependent frequency that was associated with significantly lower levels of apoC-III protein, a favorable lipoprotein profile and increased longevity (Atzmon et al. 2006). In contrast to the Amish and Ashkenazi apoC-III polymorphisms associated with lower plasma TG, apoC-III polymorphisms associated with higher plasma TG have also been recently described (Petersen et al. 2010). In a cohort of lean (mean body mass index [BMI] = 24.7 ± 3.6 kg/m^2) Asian Indians, carriers of apoC-III variant alleles (C-482T, T-455C, or both) were noted to have significantly higher plasma apoC-III and TG levels, and decreased ability to clear postprandial plasma TG from the circulation. Taken together, the available data strongly support the development of a therapy that reduces plasma apoC-III levels in order to reduce the very high circulating triglyceride and chylomicron levels that are accompanied by increasing risk for acute pancreatitis.

Given the profound reductions in TGs observed with volanesorsen treatment in FCS patients who have no detectable LPL activity (See Section 2.3.4), and the mechanistic data available to date on apoC-III function, potential mechanisms that explain how apoC-III inhibition results in triglyceride reduction in FCS patients include: (1) enhancing the very small residual amounts of LPL activity that these patients may have, below the limit of detection of the assay in many cases (2) potentially enhanced activity of other lipases also involved in the metabolism and breakdown of TGs, such as hepatic lipase or endothelial lipase (Kinnunen and Ehnolm 1976), and (3) apoC-III interaction with Apolipoprotein E (apoE), an important factor in liver reuptake of lipid particles by blocking apoE-mediated uptake of lipid particles in the liver (Breyer et al. 1999), and therefore, reducing apoC-III might enhance apoE-mediated uptake of lipid particles. Volanesorsen-mediated reduction of apoC-III could be contributing to one or all of these mechanisms resulting in the observed potent and sustained reductions in TG.

Through a novel apoC-III lowering mechanism of action, volanesorsen may provide the potential to manage triglyceride levels in FCS patients.

2.3 Volanesorsen

2.3.1 Mechanism of Action

Volanesorsen is a second-generation antisense oligonucleotide (ASO) drug targeted to human apoC-III. It is complementary to a region within the 3′ untranslated region of the apoC-III messenger ribonucleic acid (mRNA) and binds to the mRNA by Watson and Crick base pairing.

The hybridization (binding) of volanesorsen to the cognate mRNA, results in the RNase H1-mediated degradation of the apoC-III mRNA, thus preventing production of the apoC-III protein. Maximal antisense-mediated reduction of target mRNA levels is typically greater than 90% of control levels in sensitive tissues (Crooke and Bennett 1996; Zhang et al. 2010). Furthermore, reduction in target mRNA levels using this approach correlates directly with a subsequent reduction in target protein levels.

2.3.2 Chemistry

Chemically, volanesorsen is a synthetic oligomer of 20 nucleotides (i.e., a 20-mer) that are connected sequentially by phosphorothioate linkages. The nucleotide sequence of volanesorsen (Figure 2) is complementary to a 20-nucleotide stretch within the 3′ untranslated region of the apoC-III mRNA transcript at base position 489-508. Structurally, the oligonucleotide has 3 regions. Two (2) of them, the 5 nucleotides at the 5′ end and the 5 nucleotides at the 3′ end, are composed of 2′-*O*-(2-methoxyethyl) (MOE)-modified ribonucleotides. These MOE-modified nucleotides confer (1) increased affinity to the target mRNA (Altmann et al. 1996; McKay et al. 1999), (2) increased resistance to exonucleases and endonucleases (thereby increasing stability in tissue) (Geary et al. 2003), and (3) amelioration of some of the high dose toxicities thereby resulting in an improved safety profile compared to first generation antisense drugs containing phosphorothioate modified oligodeoxynucleotides (DNA) (Henry et al. 2000). The third region, the central portion of the oligonucleotide, is composed of 10 oligodeoxynucleotides. This chimeric design is called a MOE-Gapmer, and volanesorsen employs this chimeric structure to enable use of the RNase H1-mechanism for antisense activity. This is because while the 2′-MOE modification confers increased stability and affinity, it does not support RNase H1 catalysis of RNA hybridized to 2′-MOE-modified nucleotides (McKay et al. 1999). This is caused by conformational changes induced in the heteroduplex by 2′-alkoxy:RNA hybrids that are not recognized by RNase H1 enzymes (Inoue et al. 1987; Monia et al. 1993). By limiting the 2′-MOE modification to nucleotides flanking the phosphorothioate oligodeoxynucleotide core, the beneficial attributes of the 2′-MOE chemistry are preserved while also retaining RNase H1 recognition.

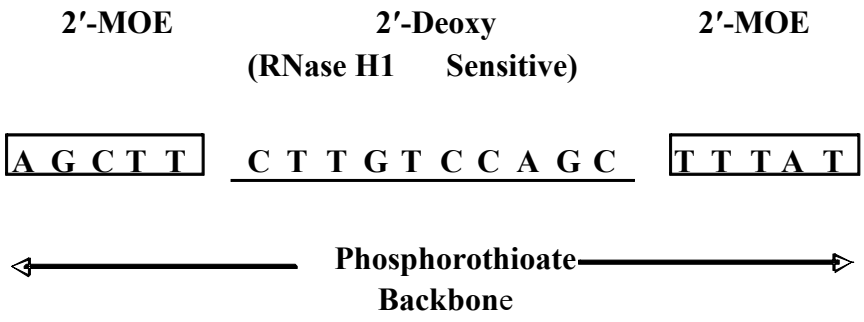


Figure 2 Design of Chimeric 2′-MOE Phosphorothioate Oligonucleotides (MOE-Gapmer). The sequence of volanesorsen is shown

2.3.3 Preclinical Experience

Inhibition of apoC-III using volanesorsen has been shown to potently reduce hepatic apoC-III mRNA as well as plasma apoC-III protein and TG in a dose- and time-dependent fashion in several species, including human apoC-III transgenic mice, and other rodent and monkey models. Treatment with volanesorsen also resulted in reduced VLDL and chylomicron TG and reduced postprandial TG in hypertriglyceridemic monkeys (Graham et al. 2013).

The pharmacokinetics (PK) and toxicity of volanesorsen have been assessed in mice, rats, and cynomolgus monkeys. General toxicity studies with volanesorsen for up to 39 weeks of treatment followed by up to a 20-week recovery period are complete. The preclinical toxicology program for volanesorsen consists of single dose safety pharmacology studies in the monkey (cardiovascular) and mouse (neurobehavioral and pulmonary assessment studies), *in vitro* and *in vivo* genetic toxicity assessment, repeat dose fertility and/or developmental reproductive toxicology studies in the mouse and rabbit and evaluation in the *in vitro* human Ether-á-go-go-related gene (hERG) assay.

Volanesorsen treatment-related findings in mice and monkeys were generally consistent with those expected for the 2′-MOE-class of ASOs. Treatment-related findings included effects consistent with drug accumulation in tissues in rodents and monkeys, species-dependent proinflammatory response in rodents and monkeys and complement activation and reductions in platelet counts in the monkey. In the mouse and monkey general toxicity studies, reduction of hepatic apoC-III mRNA (> 75%) was not associated with any findings that could be considered related to the pharmacologic inhibition of apoC-III for up to 39 weeks of treatment.

The long-term, chronic toxicology studies in rodents with volanesorsen produced a significant proinflammatory response that led to subsequent effects on the heart at high doses. The rodent species are most sensitive to the proinflammatory effects of antisense molecules. Importantly, these effects on the heart were not observed in the monkey chronic toxicity studies even at the highest doses tested where drug exposure was higher than that in rodents.

Because these changes were not observed in monkeys, the findings in the heart are considered to be rodent-specific and not relevant to humans. Nevertheless, such effects will be monitored by measurement of echocardiograms that will be included in this clinical study.

Volanesorsen caused no untoward effects in safety pharmacology studies (*in vitro* and *in vivo*) and was non-genotoxic (*in vitro* and *in vivo*). Volanesorsen had no effects on fertility or embryo/fetal development in the mouse or rabbit reproductive toxicity studies. In these studies, volanesorsen was detected in placental tissue but not in fetal tissue indicating that little, if any, drug was able to cross the placenta to reach the fetus. Reduction of apoC-III mRNA (64% in males and 47% in females) also did not affect fertility or cause untoward effects on embryo/fetal development in mice.

Detailed information concerning the preclinical studies conducted with volanesorsen can be found in the volanesorsen Investigator's Brochure.

2.3.4 Clinical Experience

Detailed information concerning the clinical studies conducted with volanesorsen can be found in the volanesorsen Investigator's Brochure. A summary is included below.

Volanesorsen has been evaluated in one Phase 1 study and two Phase 2 studies, all double blinded and placebo controlled. The total exposures comprise 99 patients and healthy volunteers administered volanesorsen from 50 to 400 mg subcutaneously up to 3 months (compared to 37 administered placebo).

All clinical trials of volanesorsen have shown large and clinically meaningful reductions in fasting plasma apoC-III and TG (~80% and 70%, respectively, mean reduction from baseline with 300 mg dose) with a very high degree of consistency of response between the different patient groups. This includes healthy volunteers, patients with moderate to severe hypertriglyceridemia not on background TG-lowering therapy, patients with moderate to severe hypertriglyceridemia on a background stable fibrate therapy (Gaudet et al. 2015), patients with FCS, and patients with T2DM.

In a Phase 2 study, 3 patients with FCS were treated with 300 mg/wk volanesorsen in an open label fashion. These patients had a mean baseline fasting TG level of 1,844 mg/dL and all 3 patients achieved TG levels below or close to 500 mg/dL during the dosing period out to Day 92 (Figure 3). Two (2) of the FCS patients had an absolute reduction in fasting TG in excess of 1,500 mg/dL (Gaudet et al. 2014).

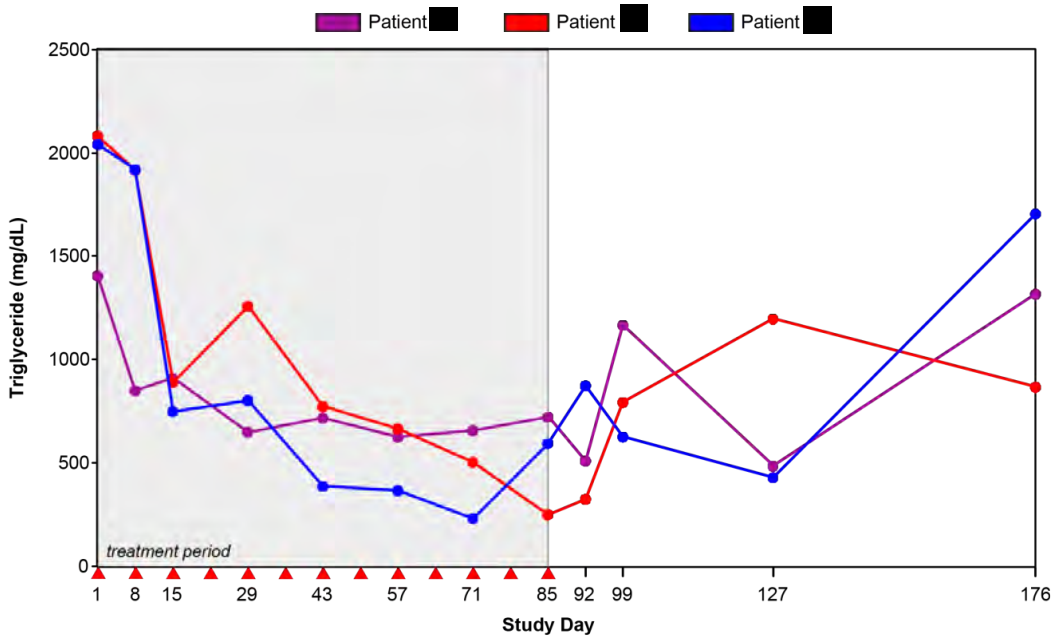


Figure 3 Fasting Triglycerides in Patients with FCS Treated with Volanesorsen

In clinical studies conducted to date volanesorsen has been well-tolerated and has shown a favorable safety profile. There has been no clinical or laboratory evidence of drug-drug interactions.

To date, there have been no volanesorsen associated laboratory abnormalities suggestive of an effect on the renal (serum creatinine, proteinuria) or hepatic systems (alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin) despite many patients in the Phase 2 clinical trials receiving concomitant medications that are known to be associated with elevations in hepatic enzymes, such as fibrates and statins. In Phase 2 studies, there was a mild decrease of platelet count associated with volanesorsen administration that recovered in the post-treatment period and was not associated with platelet-related adverse events (AEs).

The most frequently observed AEs with volanesorsen were local reactions at the injection site. Local cutaneous reactions at the injection site defined as those events presenting as either pain, tenderness, erythema, pruritus or swelling occurring on the day of injection and persisting for at least 2 days were infrequent (~15% of injections), were almost always mild, resolved spontaneously, were non-progressive, and were not associated with systemic sequelae.

2.4 Rationale for Dose and Schedule of Administration

The dose and schedule selected for this study is 300 mg per week for 52 weeks. The dose of 300 mg per week is supported by both the cumulative nonclinical data available to date and the Phase 2 clinical data. In nonclinical studies, volanesorsen treatment-related effects in rodents and monkeys were consistent with drug accumulation in tissues and also include species-specific proinflammatory responses. In the monkey, the No-Observed-Adverse-Effect Level (NOAEL) was defined by the cumulative clinical pathology results and histopathology data which provide an adequate clinical margin. No nonclinical findings were considered to be related to the pharmacologic inhibition of apoC-III.

The safety data to date suggest that volanesorsen has been well-tolerated at dose levels up to 300 mg in patients with high triglycerides (including type 2 diabetes patients and administration in combination with fibrates and statins) with the most common AEs being local to the injection site and predominantly mild. A pooled analysis of safety for the Phase 2 studies did not demonstrate any clear difference in safety or tolerability between the different doses tested (100 mg, 200 mg, and 300 mg per week for 13 weeks).

Analysis of the cohorts in which volanesorsen was studied at different doses demonstrates dose-dependent pharmacology with respect to pharmacodynamic (PD) effect on the target, apoC-III, with a clear difference in the TG-lowering effect between the different doses in the 100 mg to 300 mg dose range as compared to placebo.

In addition to the nonclinical and clinical experience of volanesorsen, the dose and schedule of administration is supported by the preclinical and clinical safety experience of several other 2′-MOE-modified ASOs that have been safely administered intravenously and subcutaneously in multiple clinical studies at doses up to 1000 mg and for treatment durations that exceed 24 months (Santos et al. 2015).

3. EXPERIMENTAL PLAN

3.1 Study Design

This is an open-label extension to the Phase 3 study of volanesorsen in patients with FCS (ISIS 304801-CS6 or ISIS 304801-CS16). Up to approximately 70 patients will receive 300 mg once weekly volanesorsen for 52 weeks.

Following the Week 52 visit, patients enter a 13-week post-treatment evaluation period.

3.2 Number of Study Centers

This study will be conducted at multiple centers worldwide.

3.3 Number of Patients

Up to approximately 70 patients will be dosed.

3.4 Overall Study Duration and Follow-up

The Study will consist of the following periods:

- A qualification period of up to 2 weeks (unless approved by the Sponsor). Please refer to Section 4.1 and Appendix A.
- A 52-week treatment period during which volanesorsen will be administered as a once weekly SC injection
- A 13-week post-treatment evaluation period

Please refer to the Schedule of Procedures in Appendix A.

3.4.1 Qualification

A period of up to 2 weeks is given to complete qualification assessments outlined in the Schedule of Procedures (Appendix A).

3.4.2 Treatment

The treatment period is 52 weeks. Eligible patients will report to the Study Center for assessments at specified intervals throughout the 52-week treatment period as detailed in the Schedule or Procedures (Appendix A). During the treatment period, volanesorsen is administered by SC injection once weekly.

3.4.3 Post-Treatment

The post-treatment evaluation period is 13 weeks and consists of 2 Study Center visits on Weeks 58 and 65.

3.5 End of Study

The end of study is last patient, last visit.

3.6 Data and Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) will review (as needed) safety, tolerability and efficacy data collected on volanesorsen during this study. Based on its ongoing assessment of the safety and tolerability of volanesorsen, the DSMB will provide recommendations to the Sponsor for modifying, stopping or continuing the study as planned. Details on the safety assessments, frequency of review and meeting schedules are outlined in the DSMB Charter and/or the statistical analysis plan (SAP).

4. PATIENT ENROLLMENT

4.1 Qualification

Before patients may be enrolled into the study, the Sponsor requires a copy of the Study Center's written independent ethics committee/institutional review board (IEC/IRB) approval of the protocol, informed consent form, and all other patient information.

Patients or their legally acceptable representatives must sign the consent form before any study-specific procedures or evaluations related to this open label study are performed. During the qualification period, the eligibility of the patient to continue in the extension study will be determined. Final assessments from the ISIS 304801-CS6 or ISIS 304801-CS16 studies may be used for qualification. A period of up to 2 weeks after completion of the ISIS 304801-CS6 or ISIS 304801-CS16 index studies (unless approved by the Sponsor) is given to complete qualification. Qualified patients will retain the unique patient identification number that was assigned to them during the ISIS 304801-CS6 or ISIS 304801-CS16 index studies. The patient identification number will be used to identify the patient throughout the extension trial and must be used on all study documentation related to that patient. The patient identification number must remain constant throughout the extension trial.

4.2 Enrollment

Patients will be enrolled after all qualification assessments have been completed and after the Investigator has verified that they are eligible per criteria in Sections 5.1 and 5.2. No patient may begin treatment prior to enrollment.

Eligible patients will be enrolled using an Interactive Voice/Web-Response System (IXRS).

5. PATIENT ELIGIBILITY

To be eligible to participate in this study candidates must meet the following eligibility criteria within 2 weeks of Study Day 1, or at the time point specified in the individual eligibility criterion listed.

5.1 Inclusion Criteria

1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law
2. Age ≥ 18 years at time of informed consent
3. Satisfactory completion of ISIS 304801-CS6 or ISIS 304801-CS16 (index studies) with an acceptable safety profile, per Sponsor and Investigator judgement. Patients who are

enrolled in ISIS 304801-CS16 must also meet the following criteria in order to enter into the Extension Study:

a. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG measurement ≥ 880 mg/dL (10 mmol/L)

b. A diagnosis of Familial Chylomicronemia Syndrome (Type 1 Hyperlipoproteinemia) by documentation of at least one (1) of the following:

- Confirmed homozygote, compound heterozygote or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as LPL, apoCII, GPIHBP1, or LMF1)
- Post heparin plasma LPL activity of ≤ 20% of normal

c. Fasting TG ≥ 750 mg/dL (8.4 mmol/L) at Screening for the ISIS 304801-CS16 study.

4. Able and willing to participate in a 65-week study
5. Satisfy one (1) of the following:

a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved), abstinent, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration.

b. Males: Surgically sterile, abstinent or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration.

5.2 Exclusion Criteria

1. Have any new condition or worsening of existing condition which in the opinion of the Investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study.
2. Unwilling to comply with lifestyle requirements for the duration of the study (Section 6.3).

6. STUDY PROCEDURES

6.1 Study Schedule

All required study procedures are outlined in Appendices A, B, C, and D.

6.1.1 Qualification

Please refer to Section 4.1 and Appendix A.

6.1.2 Treatment Period

The patients, Investigators, study staff, and the Sponsor will remain blinded to lipid data through the last patient's Week 13 visit of the extension study or until results from the database locks for the ISIS 304801-CS6 and ISIS 304801-CS16 index studies become available, whichever comes first.

During the treatment period, patients will report to the study center for clinic visits a minimum of 10 times during Weeks 1-52 (see Schedule of Procedures in Appendix A). Study Drug will be administered once weekly (Section 8.1). Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), AEs, concomitant medication/procedure information, lipid panel, volanesorsen plasma concentrations, immunogenicity (IM) testing, liver/spleen MRI, ECGs, echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Adverse events at the injection site should be collected as adverse events. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period and all patients will complete a daily food diary for one week prior to their quarterly visit. All blood and urine samples should be collected prior to volanesorsen administration. Blood sampling for lipid panels at Weeks 12, 25, and 51 may be conducted by a clinical service if more convenient for the patient. Approval for study procedures to be conducted by a clinical service on other outpatient visit days will require prior approval by the Sponsor. Patients must be fasted prior to drawing all blood samples and samples drawn locally must be sent to the central laboratory for analysis. Every effort should be made to ensure the previous week's dose is given 7 days prior to a scheduled clinic visit. Dosing instructions and training will be provided to the patient where applicable.

All reasonable attempts should be made to ensure compliance with the visit schedule as outlined in Appendix A. However, in the event that a visit does not occur or is delayed, all subsequent visits should be calculated based on the time elapsed since Day 1 rather than from the date of the previous visit.

6.1.3 Pharmacokinetic (PK) Subgroup

A subgroup of patients will participate in an extended PK collection. Patients in this subgroup will have more frequent PK sampling over a 24-hour period following the first dose on Study Day 1 in order to evaluate the plasma PK parameters of volanesorsen. Patients in this subgroup will have an additional visit to the clinic on Day 2 to collect a 24-hour post-dose blood draw after dosing on Day 1. The detailed PK sampling schedules are outlined in Appendix C.

Participation in the PK subgroup is optional for sites and patients, and consent may be withdrawn for the subgroup-specific procedures (e.g., multiple blood draws for PK) without being withdrawn from the study. If a patient withdraws consent from the subgroup procedures, he/she should remain on study and continue to follow all the non-subgroup assessments and procedures as outlined in Appendix A.

6.1.4 Post-Treatment Period

After completion of the Week 52 visit assessments, patients will enter the 13-week post-treatment evaluation period. This period consists of 2 Study Center visits on Weeks 58 and 65 as outlined in the Schedule of Procedures in Appendix A.

6.2 Additional Study Assessments

6.2.1 Laboratory Assessments

Laboratory analyte samples will be collected throughout the study.

A list of these analytes is contained in Appendix B.

6.2.2 Physical Exams and Vital Signs

Physical exams and vital signs will be performed as indicated in the Schedule of Procedures (Appendix A). Vital signs should include weight, blood pressure, pulse rate, respiratory rate and body temperature. Blood pressure and pulse rate will be recorded after the patient has been in a sitting position for at least 5 minutes. Semi-supine systolic and diastolic blood pressure should always be measured on the same arm (preferentially on the left arm). Height will be measured at the Day 1 visit.

6.2.2.1 Eruptive Xanthoma

At each visit, patients will be asked whether they have had any episodes of eruptive xanthoma since their last visit and the number/duration of the events will be recorded. Physical exams should also include skin examination for presence/resolution of eruptive xanthomas. If a patient experiences an episode of eruptive xanthoma during the study, photos of the area should be taken, if possible.

6.2.2.2 Lipemia Retinalis

If possible, lipemia retinalis will be assessed by fundus photography prior to administration of the first dose of Study Drug and repeated at Week 52. Images will be evaluated by an independent assessor, blinded to the patient's treatment assignment.

6.2.3 Echocardiography

Echocardiography for assessment of left and right ventricular function and mitral and aortic valve function will be conducted at Week 26 and Week 52 in all patients. For the purpose of assessment of treatment-emergent changes, all echocardiograms will be evaluated on an ongoing basis by an independent central reader. Results will be provided to the DSMB for their review.

6.2.4 ECG

The ECG will be recorded after the patient has been resting in a supine position for at least 5 minutes. ECGs will be performed in triplicate at Week 13, Week 26, Week 38, Week 52, and Week 65.

6.2.5 MRI

MRI of the liver and spleen will be conducted at Week 52 for all patients for whom MRI is not contraindicated, e.g., patients having metal implants.

MRIs will be conducted using standardized procedures and settings. MRIs will be read by an independent central reader to assess liver fat and liver and spleen size**.**

6.2.6 Quality of Life Assessments

All patients will complete Quality of Life Questionnaires (EQ-5D and SF-36) at Week 13, Week 26, Week 52, and Week 65.

6.2.7 Disease Symptom Diary

All patients will complete a symptom questionnaire once a week starting at the beginning of the qualification period and continuing to the end of the post-treatment follow-up period.

6.2.8 Diet Monitoring

The diets of patients enrolled in the study will be monitored as follows:

1. All patients will be required to maintain a 7-day food diary prior to Week 1, Week 13, Week 26, Week 52, and Week 65.
2. Patients will receive diet/alcohol counseling by qualified study personnel at clinic visits throughout the course of the study. Qualified study personnel will telephone the patient to provide diet/alcohol counseling for visits that are conducted by a clinical service.
3. In addition to the 7-day food diary and the diet /alcohol counseling during clinic visits, telephone calls from a dietitian or qualified study personnel to assess as to how each patient is maintaining their diet will be conducted randomly during the treatment and post treatment follow-up periods.

6.2.9 Family History

Family history of hypertriglyceridemia and pancreatitis will be collected for each patient.

6.3 Restriction on the Lifestyle of Patients

6.3.1 Contraception Requirements

All male patients and women of childbearing potential must refrain from sperm/egg donation and practice effective contraception from the time of signing the informed consent form until at least 13 weeks after their last dose of study treatment.

Male patients must also encourage their female partner to use effective contraception from the time of signing the informed consent until 13 weeks after the subject's last dose of study treatment.

For the purposes of this Study, women of childbearing potential are defined as any female who has experienced menarche, and who does not meet one (1) of the following conditions:

- Postmenopausal: 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved
- 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Post hysterectomy

For the purposes of the study, effective contraception is defined as follows:

For male patients:

- Effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the use of condoms together with spermicidal foam/gel/film/ cream/suppository. Male patients must also encourage their female partner to use effective contraception from the time of signing the informed consent until 3 months after the patient's last dose of study treatment. Effective contraceptive for the female partner includes: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or barrier methods (female condom*, diaphragm, sponge, cervical cap) together with spermicidal foam/gel/film/cream/suppository. Male patients with partners that are pregnant must use condoms to ensure that the fetus is not exposed to the Study Drug.

For female patients:

- Using one (1) or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or any 2 barrier methods (a combination of male or female condom* with diaphragm, sponge, or cervical cap) together with spermicidal foam/gel/film/cream/suppository.

*Note: A female condom and a male condom should not be used together as friction between the two can result in either product failing.

6.3.2 Other Requirements

All patients will be required to fast for at least 10 hours before visits requiring fasted blood sampling.

All patients will be encouraged to follow a diet comprising ≤ 20 g fat per day during the study.

Alcohol should not be consumed during the study.

All patients will be given an instruction card that must be presented to the treating physician if a suspected case of pancreatitis occurs. The card will explain that the patient is in a clinical trial and that serum lipase and/or amylase measures should be done in order to adjudicate the event, based on Atlanta Classification (Banks et al. 2013). If serum or amylase activity is less than 3 x upper limit of normal (ULN), imaging, preferably contrast-enhanced computed tomography, should be considered to confirm the diagnosis of acute pancreatitis per the Atlanta Criteria.

7. STUDY DRUG

7.1 Volanesorsen Description

Volanesorsen drug product (ISIS 304801) characteristics are listed in Table 1.

Volanesorsen (ISIS 304801) is contained in glass prefilled syringes (PFS). Volanesorsen and its storage and preparation instructions will be provided by the Sponsor or designee. Volanesorsen must be stored securely at 2° to 8° C and be protected from light.

Table 1 Volanesorsen (ISIS 304801) Characteristics

Strength	200 mg/mL
Volume/Formulation	1.5 mL solution per PFS
Dose	300 mg once weekly
Route of Administration	SC

7.2 Packaging and Labeling

The Sponsor will provide the Investigator with packaged volanesorsen labeled (ISIS 304801) in accordance with specific country regulatory requirements.

7.3 Study Drug Accountability

The study staff is required to document the receipt, dispensing, and return/destruction of volanesorsen provided by the Sponsor. The Study Center must return all unused volanesorsen to the Sponsor or designee. All used syringes must be disposed of as per the site's hazardous waste destruction policy.

8. TREATMENT OF PATIENTS

8.1 Volanesorsen Administration

For each individual patient, volanesorsen will be administered subcutaneously as a single 1.5 mL injection once weekly for Weeks 1-52.

Patients should receive one (1) dose per week, with weeks always defined relative to Study Day 1. For example if a patient receives the first dose on a Monday, subsequent doses should be given on Mondays, if possible. If a patient misses an injection, or if dosing on the usual day is not possible, the patient can reschedule the injection provided that 2 doses are administered at least 2 days apart.

Every effort should be made to ensure the previous week's dose is given 7 days prior to a scheduled clinic visit.

Please refer to the Study Drug Manual provided by the Sponsor for more detailed instructions for volanesorsen preparation and administration.

8.2 Other Protocol-Required Drugs

There are no other protocol-required drugs (Section 6.2.5).

8.3 Other Protocol-Required Treatment Procedures

There are no other protocol required treatment procedures for this study.

8.4 Treatment Precautions

There are no specific treatment precautions required for this study.

8.5 Safety Monitoring Rules

Please refer also to the 'Guidance for Investigator' section of the Investigator's Brochure.

For the purposes of safety monitoring baseline is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 (e.g., qualification assessments or assessments from the final visits of ISIS 304801-CS6 and ISIS 304801-CS16 index studies if used for qualification).

In addition to the standard monitoring of clinical safety parameters, the following guidelines are provided for the monitoring of selected parameters chosen based on preclinical and clinical observations.

Confirmation Guidance: At any time during the study (Treatment or Post-Treatment Periods), the initial clinical laboratory results meeting the safety monitoring or stopping criteria presented below **must be confirmed** by performing measurements (ideally in the same laboratory that performed the initial measurement) on new specimens. All new specimen collections should take place as soon as possible (ideally within 3 days of the initial collection). For stopping rules, if the initial laboratory result is observed during the Treatment Period, the results from the retest **must be available** prior to administering the next dose of volanesorsen.

In addition to the safety monitoring parameters listed below, the Sponsor may request confirmation of additional lab values.

Re-dosing Guidance: Patients with initial laboratory test values that reach a stopping rule must not be re-dosed until the re-test results are available. In general, patients who do not meet the stopping rules based upon retest may continue dosing. However, the Investigator and the Sponsor Medical Monitor (or appropriately qualified designee) should confer as to whether additional close monitoring of the patient is appropriate. If any of the stopping criteria described below (refer to Sections 8.6.1 to 8.6.3) are met, the patient will be permanently discontinued from further treatment with volanesorsen, evaluated fully as outlined below and in consultation with the Sponsor Medical Monitor or appropriately qualified designee, and will be followed up in accordance with Section 8.8 of the protocol.

8.5.1 Safety Monitoring Rules for Liver Chemistry Tests

The following rules are adapted from the draft guidance for industry, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," issued by the U.S. Department of Health and Human Services, Food and Drug Administration, July 2009. For a definition of Baseline please refer to guidance in Section 8.5 above.

In the event of an ALT or AST measurement that is > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) at any time during the study (Treatment or Post-Treatment Period), the initial measurement(s) should be confirmed as described above. Additional confirmatory measurements should also be performed if ALT or AST levels increase to 5 x ULN.

Frequency of Repeat Measurements: Patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) should have their liver chemistry tests (ALT, AST, alkaline phosphatase (ALP), international normalized ratio (INR) and total bilirubin) retested at least once-weekly until ALT and AST levels become ≤ 1.2 x ULN or 1.2 x baseline value if the baseline value was > ULN.

Further Investigation into Liver Chemistry Elevations: For patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), the following evaluations should be performed:

1. Obtain a more detailed history of symptoms and prior and concurrent diseases
2. Obtain further history for concomitant drug use (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
3. Obtain a history for exposure to environmental chemical agents and travel
4. Serology for viral hepatitis (HAV IgM, HBsAg, HCV antibody, CMV IgM, and EBV antibody panel)
5. Serology for autoimmune hepatitis (e.g., antinuclear antibody [ANA])

Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic CT or MRI scans, may be performed at the discretion of the Investigator, in consultation with the Sponsor Medical Monitor. Repetition of the above evaluations should be considered if a patient's ALT and/or AST levels reach 5 x ULN.

8.5.2 Safety Monitoring Rules for Platelet Count Results

If a patient's platelet count falls by 30% or greater from baseline and the absolute platelet count is 75,000/mm^3 or less, then the patient's platelet counts should be monitored more frequently. In the event of any significant fall in platelet count, the frequency of monitoring and additional lab tests will be determined by the Sponsor Medical Monitor or designee in consultation with the Investigator.

8.5.3 Safety Monitoring for Minor Bleeding Events

Minor bleeding events are those that do not fulfill the criteria for major bleeding or clinically relevant, non-major bleeding events (which are defined in Section 8.6.3), for example excess bruising, petechiae, gingival bleeding on brushing teeth. If a minor bleeding event occurs, the Investigator must notify the Sponsor Medical Monitor and additional testing of coagulation parameters activated partial thromboplastin time (aPTT), prothrombin time (PT), INR and platelet count should be performed.

8.5.4 Safety Monitoring for Constitutional Symptoms

Patients will be instructed to promptly report any signs of symptoms of fever or constitutional symptoms that may arise during the study and the Investigator should closely evaluate all potential causes, including concomitant illness. Patients that experience persistent constitutional symptoms should be discussed with the Sponsor Medical Monitor or designee to determine whether additional monitoring or laboratory tests are required.

8.5.5 Safety Monitoring for LDL-C Elevations

Beginning at Week 13, laboratory alerts will be in place to notify the Investigator if a patient has a low-density lipoprotein-cholesterol (LDL-C) > 160 mg/dL (> 130 mg/dL for patients with T2DM) on 2 consecutive visits. If this occurs, LDL-C values for this patient will be unblinded for the remainder of the study and the Investigator will be encouraged to initiate/adjust treatment to lower LDL-C according to country-specific guidelines (e.g., initiate statin therapy or increase the statin dose for patients who are already on treatment).

8.5.6 Safety Monitoring for Insulin, Oral Antidiabetic Medication and Glucose

Patients on insulin will monitor their glucose levels with a glucometer as per standard practice guidelines and bring their glucometer or glucometer log printout to every clinic visit.

- The Investigator or delegate will review the glucometer reading or printout at every clinic visit to evaluate if fasting pre-breakfast self-monitored plasma glucose values exceed threshold values as per the Safety Monitoring Rules for Hyperglycemia below.

All diabetic patients will note any changes in their insulin dose and /or oral antidiabetic therapy, as well as any hypoglycemic episode they may experience.

- The Investigator or delegate will ask patients at every clinic visit if they made changes in their insulin dose or oral antidiabetic therapy, and if they experienced a hypoglycemic episode.
    - Patients will be instructed on the monitoring and management of hypoglycemic episodes at each visit.
    - Documented symptomatic hypoglycemic episodes should be captured as adverse events in the adverse event CRF. Documented symptomatic hypoglycemia is defined as typical hypoglycemia symptoms accompanied by measured plasma glucose ≤ 70 mg/dL (≤ 3.9 mmol/L.
    - Any changes in insulin dose or oral antidiabetic therapy should be captured into the Concomitant Medication CRF.

8.5.7 Safety Monitoring Rule for Documented Severe Hypoglycemia

A **documented severe hypoglycemic event** is defined as one (1) in which the patient requires assistance of another person to obtain treatment for the event and has a plasma glucose level ≤ 70 mg/dL (≤ 3.9 mmol/L). The rescue treatment of hypoglycemia may include IV glucose or buccal or intramuscular glucagon.

The definition of severe symptomatic hypoglycemia includes all episodes in which neurological impairment was severe enough to prevent self-treatment and which were thus thought to place patients at risk for injury to themselves or others. Note that “requires assistance” means that the patient could not help himself or herself. Someone being kind that assists spontaneously the patient when not necessary does not qualify as “requires assistance.”

Severe hypoglycemia will be qualified as a SAE only if it fulfills SAE criteria.

If a patient presents with symptoms of hypoglycemia, the Investigator will need to take immediate action to confirm the patient's glucose level and treat the patient accordingly.

The experience of hypoglycemia may vary greatly from patient to patient. However, there are certain classical signs and symptoms, of which patients should be aware as a clue that their blood glucose may be low. Common symptoms include headache, heart pounding, confusion, disorientation, numbness or tingling, pale skin, shakiness or tremulousness, increased appetite, anxiousness or nervousness, lightheadedness or dizziness, sweating, and weakness. Many of these symptoms are listed in the diary provided to patients. These diaries will be used only to assist the Investigator in assessing the event. Appropriate source documentation should capture the necessary information on the event with the aid of the diaries. Patients must be given adequate instructions on the use of the diaries.

If patients suspect they might be having a hypoglycemia reaction, they should check their blood glucose using their meters as soon as possible, before treatment if possible, provided they feel it is safe to do so. If there is doubt about safety they should treat the event first, using some sugar, milk, or juice for example, then obtain and record a blood glucose value as soon as possible thereafter. The time and nature of treatment should be noted, and especially if any blood glucose result was before or after treatment. It would be helpful for the patient to note if a contributory factor (e.g., missed or reduced meals, unaccustomed physical activity) occurred earlier in the day of the event.

8.5.8 Safety Monitoring for Hyperglycemia

Upward dose titration and/or addition of any other anti-hyperglycemic agent(s) will not be allowed during the course of the study, unless specific threshold values are met at Week 13 or later and confirmed on subsequent testing (ideally within one (1) week of the initial test).

HbA1c is monitored every 3 months throughout the study. In addition, patients on insulin should self-monitor their plasma glucose (SMPG) routinely on a glucometer as per practice guidelines. If a fasting pre-breakfast SMPG value exceeds the specific glycemic limit, the patient should check it again on the following 2 days. If all the fasting pre-breakfast values on 3 consecutive days exceed the specific limit, the patient should contact the Investigator and an unscheduled central laboratory FPG measurement and HbA1c should be performed.

The threshold values are defined as:

- FPG > 270 mg/dL (15.0 mmol/L)
- HbA1c > 9% (for patients with baseline HbA1c < 8% and HbA1c increase of more than 1% from baseline (for patients with baseline HbA1c ≥ 8 and < 9%)

In case of confirmed FPG/HbA1c above the threshold value, the Investigator should ensure that no reasonable explanation exists for insufficient glucose control and in particular that:

- Plasma glucose was actually measured in the fasting condition (i.e., after at least 10 hours fast)
- Absence of intercurrent disease which may jeopardize glycemic control. In case of an emergency (e.g., surgery, infection), the Investigator can take appropriate measures for glycemic control

- Compliance to treatment is appropriate
- Compliance to diet and lifestyle is appropriate

If any of the above can reasonably explain the insufficient glycemic control, the Investigator should consider the following:

- Investigation and treatment of intercurrent disease (to be reported in adverse event (AE)/concomitant medication parts of the e-CRF)
- Stress on the absolute need to be compliant to treatment
- Organize a specific interview with a Registered Dietician or other qualified nutrition professional and stress on the absolute need to be compliant to diet and lifestyle recommendations

A FPG/HbA1c follow-up assessment should be arranged after appropriate action has been taken. If none from the above-mentioned reasons can be found, or if appropriate action fails to decrease FPG/HbA1c under the threshold values, additional medication may be introduced at the Investigator's discretion and according to local guidelines after discussion with the Sponsor Medical Monitor.

8.5.9 Acute Pancreatitis

If a patient has an episode of acute pancreatitis, dosing with Study Drug should be suspended temporarily until the patient is clinically stable. The suitability of the patient for continued dosing and the need for any modification to treatment schedule (refer to Section 8.7) will be determined by the Investigator in consultation with the Study Medical Monitor.

8.6 Stopping Rules

For the purposes of stopping rules baseline is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1.

8.6.1 Stopping Rules for Liver Chemistry Elevations

In the event of laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor,** dosing of a patient with volanesorsen will be stopped permanently; values that are not confirmed due to failure to retest or missing lab values will be presumed confirmed:

1. ALT or AST > 8 x ULN, which is confirmed
2. ALT or AST > 5 x ULN, which is confirmed and persists for ≥ 2 weeks
3. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed **and** total bilirubin > 2 x ULN or INR > 1.5
4. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed, and the new appearance (i.e., onset coincides with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> ULN) felt by the Investigator to be potentially related to hepatic inflammation

8.6.2 Stopping Rules for Renal Function Test Results

In the event of a persistent elevation that is observed over 2 consecutive weeks, for any of the three criteria below, dosing of a patient with volanesorsen may be stopped temporarily:

1. Serum creatinine increase that fulfill all of the following criteria: ≥ 0.3 mg/dL (26.5 µmol/L) and ≥ 40% above baseline creatinine values and > ULN

2. Proteinuria, dipstick 2 + (confirmed by dipstick retest and then further confirmed by a quantitative total urine protein measurement of > 1.0 g/24-hour)

3. Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault ≤ 40 mL/min that is confirmed by a 24-hour urine collection

The possible dosing re-initiation or follow-up schedule for any events meeting either of these criteria will be determined by the Investigator **in consultation with** the Sponsor Medical Monitor or designee.

8.6.3 Stopping Rule for Platelet Count Results

In the event of a platelet count less than 50,000/mm^3 that is associated with major bleeding or clinically relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with volanesorsen will be stopped permanently. The follow-up schedule for any events meeting this stopping criterion will be determined by the Investigator in consultation with the Sponsor Medical Monitor.

In the event of a platelet count less than 50,000/mm^3, and in the absence of major bleeding or clinically relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with volanesorsen should be suspended temporarily until the platelet count has recovered to ≥ 100,000/mm^3. The suitability of the patient for continued dosing and the need for any modification to treatment schedule (refer to Section 8.7) will be determined by the Investigator in consultation with the Study Medical Monitor and will be based on factors such as the original rate of decline in the patient's platelet count, whether any bleeding events were experienced by the patient, and the speed of recovery of platelet count upon holding of dosing.

If after the first dosing re-challenge the platelet count again falls below 50,000/mm^3, then dosing of the patient must be held until the platelet count again returns to at least 100,000/mm^3. The suitability of the patient for continued dosing and the need for any further modification to treatment schedule or dose (refer to Section 8.7) will be re-examined by the Investigator in consultation with the Study Medical Monitor based on (at least) the factors mentioned above.

If after the second re-challenge the platelet count falls below 50,000/mm^3 and is subsequently confirmed (see Section 8.5), dosing with volanesorsen will be stopped permanently. The follow-up schedule for any events meeting this stopping criterion will be determined by the Investigator in consultation with the Study Medical Monitor.

Definition of Major Bleeding Events (Schulman et al. 2005):

- Fatal bleeding, and/or
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarterial or pericardial, or intramuscular with compartment syndrome, and/or
- Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more within 24 hours, or leading to transfusion of 2 or more units of whole or red cells

Definition of Clinically Relevant, Non-Major Bleeding Events (Schulman et al. 2005):

1. Multiple-source bleeding
2. Spontaneous hematoma > 25 cm^2
3. Excessive wound hematoma (not injection site related)
4. Macroscopic hematuria (spontaneous or lasting > 24 hours if associated with an intervention)
5. Spontaneous rectal bleeding; epitasis, gingival bleeding, hemoptysis, hematemesis
6. Bleeding after venipuncture for > 5 minutes

8.7 Adjustment of Dose Frequency

Dose adjustments, including dose interruptions, and/or decreasing the dose frequency will be allowed for safety and tolerability. Any proposed adjustment to treatment schedule must be discussed with, and approved by, the Study Medical Monitor prior to initiation. Up to 2 adjustments in the treatment schedule may be allowed for patients that are unable to tolerate the once weekly dose (for example if platelet counts fall below 50,000/mm^3 as described in Section 8.6.3). If the patient remains stable after adjustment, they may be cautiously returned to the original once weekly regimen after consultation with the Study Medical Monitor.

Patients may be dose paused in response to AEs after consultation with Study Medical Monitor.

8.8 Discontinuation of Study Treatment

A patient must permanently discontinue study treatment for any of the following:

- The patient becomes pregnant. Report the pregnancy according to instructions in Section 9.5.4
- The patient withdraws consent
- The patient experiences an AE that necessitates permanent discontinuation of study treatment
- The patient develops laboratory test abnormalities that meet any of the stopping rules listed in Section 8.6

The reason for discontinuation of study treatment must be recorded in the CRF and source documentation.

8.8.1 Follow-up Visits for Early Termination from Treatment Period

Any patient who discontinues early from the Treatment Period should be strongly encouraged to attend applicable landmark visits at Weeks 12, 13, 25, 26, and 51, 52 (calculated based on the time elapsed since Day 1) to collect fasting lipid panels and conduct safety assessments in accordance with the schedule of procedures in Appendix A. Any patient who discontinues treatment after Week 44 should also be strongly encouraged to attend a final follow-up visit (Week 65 visit assessments) approximately 13 weeks after their last dose of Study Drug, in addition to the applicable landmark visits.

If the patient declines or is unable to participate in the above, an early termination (ET) visit (Week 52 visit assessments) should be performed at the time of withdrawal, at a minimum, and ideally within 2 weeks from the last dose of Study Drug.

8.8.2 Follow-up Visits for Early Termination from Post-Treatment Follow-up Period

The patient who requests to withdraw from the study during the Post-Treatment Follow-up Period should be encouraged to undergo a final follow-up visit (Week 65, see Appendix A) prior to leaving the study.

If a patient withdraws due to an AE at any time during the study, the Investigator should arrange for the patient to have appropriate follow-up until the AE has resolved or stabilized.

8.9 Withdrawal of Patients from the Study

Patients must be withdrawn from the study for any of the following:

- Withdrawal of consent
- The patient is unwilling or unable to comply with the protocol

Other reasons for withdrawal of patients from the study might include:

- At the discretion of the Investigator for medical reasons
- At the discretion of the Investigator or Sponsor for noncompliance
- Significant protocol deviation

All efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information, including the reason for withdrawal from study, must be recorded in the CRF.

Any patient who withdraws consent to participate in the study will be removed from further treatment and study observation immediately upon the date of request. These patients should be encouraged to complete the ET study procedures and observations at the time of withdrawal (see Section 8.8 and Appendix A).

For patients withdrawn for reasons other than withdrawal of consent every effort should be made to complete the early termination study procedures and observations at the time of withdrawal (see Section 8.8 and Appendix A).

8.10 Concomitant Therapy and Procedures

The use of concomitant therapies or procedures defined below must be recorded on the patient's CRF. AEs related to administration of these therapies or procedures must also be documented on the appropriate CRF.

8.10.1 Concomitant Therapy

A concomitant therapy is any non-protocol specified drug or substance (including over-the-counter medications, herbal medications and vitamin supplements) administered between signing informed consent and completion of the post-treatment follow-up period. All concomitant medications/treatments and significant non-drug therapies (including supplements and assistive devices) received by a patient, including changes in the patient's current medications, must be recorded in the patient's source documents and CRF. Patients taking over the counter (OTC) omega-3 fatty acids should make every effort to remain on the same brand throughout the study.

Allowed Concomitant Therapy

Any medications deemed necessary by the Investigator are allowed except those listed in the disallowed concomitant therapy.

Disallowed Concomitant Therapy

No lipid lowering therapies (e.g., fibrates, niacin, fish oil or other products containing omega-3 fatty acids [including OTC preparations]), -glucagon-like peptide-1 (GLP-1) agonists, Glybera, or systemic corticosteroids may be started or adjusted after baseline qualification. Doses of existing oral anti-diabetic medication, oral contraceptives, hormone replacement therapy, anticoagulants, or drugs or dietary supplements with potential lipid-altering effects should not be adjusted. Study patients are prohibited from receiving other experimental agents during the study. This includes marketed agents at experimental dosages that are being tested for the treatment of hypertriglyceridemia.

Patients should consult with the Site Investigator or designee prior to initiating any new medication, including non-prescription or herbal compounds or any other non-drug therapy.

8.10.2 Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between signing of informed consent and Week 65 visit.

Disallowed Concomitant Procedure

Plasma apheresis is not allowed during the study.

8.11 Treatment Compliance

Compliance with treatment dosing is to be monitored and recorded by Study Center staff. The Study Center staff is required to document the receipt, dispensing, and return/destruction of volanesorsen. Patients that are self-administering volanesorsen at home must record treatment in a dosing diary that will be reviewed periodically by Study Center staff and the Clinical Monitor.

9. SERIOUS AND NON-SERIOUS ADVERSE EVENT REPORTING

9.1 Sponsor Review of Safety Information

Safety information will be collected, reviewed, and evaluated by the Sponsor in accordance with the Safety Management Plan throughout the conduct of the clinical trial.

9.2 Regulatory Requirements

The Sponsor is responsible for regulatory submissions and reporting to the Investigators of serious adverse events (SAEs) including suspected unexpected serious adverse reactions (SUSARs) per the International Conference on Harmonization (ICH) guidelines E2A and ICH E6. Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines.

Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) will be notified of any SAE according to applicable regulations. The Data and Safety Monitoring Board (DSMB) will be notified of any SAE as specified in the DSMB charter.

The Sponsor or designee will evaluate the available information and decide if there is a reasonable possibility that volanesorsen caused the AE and, therefore, meets the definition of a SUSAR.

The following table identifies the SAEs that the Sponsor or designee will not report on an individual basis in an expedited manner because they are anticipated to occur in the study population independent of volanesorsen exposure. The Investigator still has the responsibility to report all SAEs to the Sponsor as described in Sections 9.4.1 to 9.4.3.5.

Table 2 Expected Event for the Protocol Defined Population by Preferred Term and the Expected Incidence

Preferred Term	Expected Incidence in the Protocol Defined Population (Gaudet et al. 2010 and 2013)
Pancreatitis associated events including the PTs of hereditary pancreatitis, pancreatitis, pancreatitis acute, pancreatitis chronic, pancreatitis necrotizing, pancreatitis relapsing	0.2-0.35 events per patient-year

Fatal pancreatitis associated events will be considered as unexpected and are reportable. The Sponsor and DSMB will monitor non-fatal pancreatitis associated SAEs using the incidence rate of the event compared to the rate expected in a non-volanesorsen exposed population. If the aggregate analysis indicates that an event is occurring significantly more frequently or at a greater severity than expected, then the event will be reported.

SAEs not specified in the table will be evaluated on case by case basis to determine whether there is a reasonable possibility that the drug caused the event. If the event is considered by the Sponsor or designee to meet the definition of a SUSAR the event will be reported.

9.3 Definitions

9.3.1 Adverse Event

An adverse event is any unfavorable and unintended sign (including a clinically-significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the study or use of investigational drug product, whether or not the AE is considered related to the investigational drug product.

9.3.2 Adverse Reaction and Suspected Adverse Reaction

An adverse reaction is any adverse event caused by volanesorsen.

A suspected adverse reaction is any adverse event for which there is a reasonable possibility that volanesorsen drug caused the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

9.3.3 Serious Adverse Event (SAE)

A serious adverse event is any adverse event that in the view of either the Investigator or Sponsor, meets any of the following criteria:

- Results in death
- Is life threatening: that is, poses an immediate risk of death at the time of the event

An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Hospitalization is defined as an admission of greater than 24 hours to a medical facility and does not always qualify as an AE
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly or birth defect in the offspring of the patient (whether the patient is male or female)
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

9.4 Monitoring and Recording Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the study (i.e., before informed consent) should be recorded as Medical History and not recorded as AEs unless the pre-existing condition worsened. The Investigator should always group signs and symptoms into a single term that constitutes a **single unifying diagnosis** if possible.

9.4.1 Serious Adverse Events

In the interest of patient safety, and in order to fulfill regulatory requirements**,** all SAEs (regardless of their relationship to volanesorsen) should be reported to the Sponsor or designee within 24 hours of the Study Center's first knowledge of the event. The collection of SAEs will begin after the patient signs the informed consent form and stop at the end of the patient's follow-up period which is defined as the Week 65 visit. When the Investigator is reporting by telephone, it is important to speak to someone in person versus leaving a message. An Initial Serious Adverse Event Form should be completed and a copy should be faxed to the Sponsor or designee.

Detailed information should be actively sought and included on Follow-Up Serious Adverse Event Forms as soon as additional information becomes available. All SAEs will be followed until resolution. SAEs that remain ongoing past the patient's last protocol-specified follow-up visit will be evaluated by the Investigator and Sponsor. If the Investigator and Sponsor agree the patient's condition is unlikely to resolve, the Investigator and Sponsor will determine the follow-up requirement.

9.4.2 Non-Serious Adverse Events

The recording of non-serious AEs will begin after the patient signs the informed consent form and will stop at the end of the patient's follow-up period, which is defined as the Week 65 visit. The Investigator will monitor each patient closely and record all observed or volunteered AEs on the Adverse Event Case Report Form.

9.4.3 Evaluation of Adverse Events (Serious and Non-Serious)

The Investigator's opinion of the following should be documented on the Adverse Event Case Report Form:

9.4.3.1 Relationship to the Study Drug

The event's relationship to volanesorsen is characterized by one (1) of the following:

- **Related:** There is clear evidence that the event is related to the use of volanesorsen e.g., confirmation by positive re-challenge test
- **Possible:** The event cannot be explained by the patient's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and volanesorsen administration

- **Unlikely/Remote:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to volanesorsen administration and/or exposure suggests that a causal relationship is unlikely (For reporting purposes, Unlikely/Remote will be grouped together with Not Related)

- **Not Related:** The event can be readily explained by the patient's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and volanesorsen

9.4.3.2 Severity

The severity of AEs and SAEs will be graded based on criteria from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010 (refer to Appendix D). Any AE not listed in Appendix D will be graded as follows:

- **Mild:** The event is easily tolerated by the patient and does not affect the patient's usual daily activities

- **Moderate:** The event causes the patient more discomfort and interrupts the patient's usual daily activities

- **Severe:** The event is incapacitating and causes considerable interference with the patient's usual daily activities

If the event is an SAE, then all applicable seriousness criteria must be indicated (criteria listed in Section 9.3.3).

9.4.3.3 Action Taken with Volanesorsen

Action taken with volanesorsen due to the event is characterized by one (1) of the following:

- **None:** No changes were made to volanesorsen administration and dose

- **Permanently Discontinued:** Volanesorsen was discontinued and not restarted

- **Temporarily Interrupted, restarted – same dose:** Dosing was temporarily interrupted or delayed due to the AE and restarted at the same dose

- **Reduced schedule:** Dosing frequency was reduced

9.4.3.4 Treatment Given for Adverse Event

Any treatment (e.g., medications or procedures) given for the AE should be recorded on the Adverse Event Case Report Form (treatment should also be recorded on the concomitant treatment or ancillary procedures CRF as appropriate).

9.4.3.5 Outcome of the Adverse Event

If the event is a non-serious AE then the event's outcome is characterized by one (1) of the following:

- **AE Persists:** Patient terminates from the trial and the AE continues
- **Recovered:** Patient recovered completely from the AE
- **Became Serious:** The event became serious (the date that the event became serious should be recorded as the Resolution Date of that AE and the Onset Date of the corresponding SAE)
- **Change in Severity** (if applicable): AE severity changed

If the event is a SAE then the event's outcome is characterized by one (1) of the following:

- **Ongoing:** SAE continuing
- **Persists (as non-serious AE):** Patient has not fully recovered but the event no longer meets serious criteria and should be captured as an AE on the non-serious AE eCRF (the SAE resolution date should be entered as the date of onset of that AE)
- **Recovered:** Patient recovered completely from the SAE (the date of recovery should be entered as the SAE resolution date)
- **Fatal:** Patient died (the date of death should be entered as the SAE resolution date)

9.4.4 Adjudication Committees

All SAEs that occur during the study that are consistent with a major acute cardiovascular event (MACE) will be adjudicated by a blinded, independent committee as outlined in the MACE Adjudication Charter.

All AEs and SAEs that occur during the study that are consistent with an event of acute pancreatitis will be adjudicated by a blinded, independent committee according to the Atlanta classification of acute pancreatitis (Banks et al. 2013) and as outlined in the Pancreatitis Adjudication Charter. In addition, data for prior episodes of acute pancreatitis or suspected pancreatitis will be collected by review of each patient's medical chart and these events will also be adjudicated.

9.5 Procedures for Handling Special Situations

9.5.1 Abnormalities of Laboratory Tests

Clinically-significant abnormal laboratory test results may, in the opinion of the Investigator, constitute or be associated with an AE. Examples of these include abnormal laboratory results that are associated with symptoms, or require treatment, e.g., bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac arrhythmias due to hyperkalemia. Whenever possible, the underlying diagnosis should be listed in preference to abnormal laboratory values as AEs. Clinically-significant abnormalities will be monitored by the Investigator until the parameter returns to its baseline value or until agreement is reached between the Investigator and Sponsor Medical Monitor. Laboratory abnormalities deemed not clinically-significant (NCS) by the Investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator should not be deemed NCS on the laboratory sheet.

The Investigator is responsible for reviewing and signing all laboratory reports. The signed clinical laboratory reports will serve as source documents and should include the Investigator's assessment of clinical significance of out of range/abnormal laboratory values.

9.5.2 Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the patient is hospitalized; the Study Center must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the patient's consent to participate in the study
- The condition that required the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the patient's consent to participate in the study and the timing of the procedure or treatment
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission

9.5.3 Dosing Errors

Volanesorsen dosing errors should be documented as Protocol Deviations. A brief description should be provided in the deviation, including whether the patient was symptomatic (list symptoms) or asymptomatic, and the event accidental or intentional.

Dosing details should be captured on the Dosing Case Report Form. If the patient takes a dose of volanesorsen that exceeds protocol specifications and the patient is symptomatic, then the symptom(s) should be documented as an AE and be reported per Section 9.4.

Should an overdose occur, the Investigator or designee should refer to the Guidance to Investigator's section of the Investigator's Brochure and contact the Sponsor or designee within 24 hours.

9.5.4 Contraception and Pregnancy

Male patients and female patients of childbearing potential must continue to use appropriate contraception with their partners, or refrain from sexual activity, as described in Section 6.3.1.

If a patient becomes pregnant or a pregnancy is suspected, or if a male patient makes or believes that he has made someone pregnant during the study, then the Study Center staff must be informed immediately. An Initial Pregnancy Form should be submitted to the Sponsor or designee **within 24 hours** of first learning of the occurrence of pregnancy. Follow-up information including delivery or termination is reported on Follow-up Pregnancy Forms and reported within 24 hours.

Payment for all aspects of obstetrical care, child or related care will be the patient's responsibility.

Female patients: If a suspected pregnancy occurs while on the study (including follow-up), a pregnancy test will be performed. The patient with a confirmed pregnancy will be immediately withdrawn from treatment with volanesorsen. However, the patient will be encouraged to complete the post-treatment follow-up portion of the study to the extent that study procedures do not interfere with the pregnancy. Regardless of continued study participation, the study physician will assist the patient in getting obstetrical care and the progress of the pregnancy will be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the Study Center and Sponsor may require access to the mother and infant's medical records for an additional 8 weeks after birth.

Male patients: The progress of the pregnancy in a male patient's partner should be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, **the Study Center and Sponsor may request access to the mother and infant's medical records for an additional 8 weeks after birth**. Follow-up will be performed to the extent permitted by applicable regulations and privacy considerations.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints

For fasting lipid measurements, the values at Month 3 analysis time point are defined as the average of Week 12 (Day 78) and Week 13 (Day 85) fasting assessments, the values of Month 6 analysis time point is at the end of Month 6 are defined as the average of Week 25 (Day 169) and Week 26 (Day 176) fasting assessments, and the values at the Month 12 analysis time point are defined as the average of Week 51 (Day 351) and Week 52 (Day 358) fasting assessments.

10.1.1 Efficacy Endpoints

- Percent change and absolute change from baseline in fasting TG
- Frequency and severity of patient reported abdominal pain during the treatment period
- Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-HDL-C, apoB, HDL-C, apolipoprotein A-1 (apoA-1), VLDL-C, and LDL-C
- Percent change from baseline in fasting total apolipoprotein C-III
- Quality of Life questionnaires (EQ-5D, SF-36)
- Adjudicated acute pancreatitis event rate
- Other symptoms: eruptive xanthoma, lipemia retinalis

10.1.2 Safety Endpoints

- Adverse events including adjudicated events of pancreatitis and MACE

- Vital signs and weight
- Physical examinations
- Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis)
- Echocardiography
- Electrocardiograms (ECGs)
- Use of concomitant medications
- MRIs

10.2 Sample Size

No sample size calculations were performed as this is an extension study to the double-blind, placebo-controlled ISIS 304801-CS6 and ISIS 304801-CS16 studies. Approximately 70 patients may be eligible to enroll into this study.

10.3 Populations

Full Analysis Set (FAS): All patients who are enrolled and have a baseline TG assessment. The FAS represents the practically-feasible intent-to-treat (ITT) population as delineated in ICH Guideline E9.

Per Protocol Set (PPS): Subset of the FAS who received 9 of first 13 scheduled doses of volanesorsen and with no significant protocol deviations that would be expected to affect efficacy and PD assessments. The detailed criteria will be specified and finalized prior to the final database lock.

Safety Set: All patients who are enrolled and receive at least one (1) dose of volanesorsen.

PK Population: All patients who are enrolled, receive at least one (1) dose of volanesorsen, and have at least one (1) evaluable PK sample collected, analyzed, and reported.

10.4 Definition of Baseline

Definitions of baseline are given below for the purposes of the final analysis.

For fasting lipid measurements, 2 baselines are defined for each patient: ISIS 304801-CS6 or ISIS 304801-CS16 index study baseline and the baseline in this open label study, which is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 (e.g., qualification assessments or assessments from final visit of the ISIS 304801-CS6 or ISIS 304801-CS16 index studies if used for qualification).

For other measurements, baseline for patients on active treatment in the ISIS 304801-CS6 or ISIS 304801-CS16 index study will be the ISIS 304801-CS6 or ISIS 304801-CS16 index study baseline. For patients on placebo in the ISIS 304801-CS6 or ISIS 304801-CS16 index study, baseline for safety will be the last non-missing assessment prior to the first dose of Study Drug.

10.5 Interim Analysis

An interim analysis may be conducted after the last patient's Week 13 visit of the extension study or after the database of the ISIS 304801-CS6 and ISIS 304801-CS16 index studies are locked and unblinded. Both safety and efficacy information from this OLE study may be summarized during this interim analysis. Efficacy analyses will be detailed in the SAP.

10.6 Planned Methods of Analysis

All eCRF data, lab data transfers, as well as any outcomes derived from the data, will be provided in the patient data listings. Patient data listings will be presented for all patients enrolled into the study. Descriptive summary statistics including n, mean, median, standard deviation, standard error, interquartile range (25th percentile, 75th percentile), and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data by treatment group. Where appropriate, p-values will be reported. All statistical tests will be conducted using 2-sided tests with 5% Type I error rates unless otherwise stated.

All efficacy endpoints will be assessed in the FAS and PPS. All safety assessments will be performed on the Safety Set. PK endpoints will be assessed in the PK Set as applicable.

10.6.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics by treatment group. The patient disposition will be summarized by treatment group of the index studies. All patients enrolled will be included in a summary of patient disposition.

10.6.2 Safety Analysis

Treatment duration and amount of Study Drug received will be summarized by treatment group of the index studies.

Patient incidence rates of AEs will be tabulated by MedDRA system organ class, MedDRA preferred term, and treatment group of the index studies. Narratives of treatment-emergent deaths, serious and significant AEs, including early withdrawals due to AEs, will also be provided.

All treatment-emergent AEs, all treatment-emergent AEs potentially related to Study Drug, all treatment-emergent serious AEs, and all treatment-emergent serious AEs potentially related to Study Drug will be summarized.

Injection Site Reactions (ISRs) will be summarized by treatment group of the index studies, MedDRA preferred term and severity.

Independently adjudicated events of MACE and pancreatitis will be summarized by treatment group of the index studies.

Laboratory tests to ensure patient safety including chemistry panel, complete blood count (CBC) with differential, coagulation panel, IM, complement etc., will be summarized by study visits by treatment group of the index studies.

These safety variables will also be presented as change and percent change from baseline over time after Study Drug administration, as appropriate.

Vital signs, weight, ECG measures, echocardiography assessments, and MRI assessments will be tabulated by treatment group of the index studies.

10.6.3 Efficacy Analysis

Percent change and change from baseline to Month 3, Month 6, and Month 12 in fasting TG will be summarized by treatment group of the index studies. Response rate of patients with fasting plasma TG < 750 mg/dL or achieving fasting TG ≥ 40% reduction from baseline at Month 3, Month 6, and Month 12 will be summarized. Response analysis will also be conducted using a range of fasting plasma TG thresholds for determination of responder status.

Percent change and change from baseline to Month 3, Month 6, and Month 12 will also be summarized by treatment group of the index studies for other fasting lipid measures including non-HDL-C, apoB, HDL-C, apoA-1, VLDL-C, and LDL-C, total cholesterol, and fasting total apoC-III.

The incremental effects of volanesorsen on lipid measures will be explored and the association between changes in lipid parameters and total amount of drug received will be examined, as appropriate.

Frequency and severity of patient reported abdominal pain, adjudicated acute pancreatitis event rate, quality of life assessments, and comparison of other symptoms including eruptive xanthomas and lipemia retinalis will be summarized by treatment group of the index studies.

Additional details of the analyses to be conducted will be provided in the SAP.

10.6.4 Pharmacokinetic and Immunogenicity Analysis

10.6.4.1 Pharmacokinetic Analysis

For all patients, pre-dose and post-treatment volanesorsen plasma concentrations will be summarized using descriptive statistics, with stratification by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801 CS16 and IM status.

For patients in the PK subgroup only, non-compartmental PK analysis of volanesorsen will be carried out on each individual patient data set using data collected in the open label extension (OLE) study from the intensive PK subgroup, following a single dose (i.e., single-dose PK) or multiple doses (i.e., steady-state PK), depending on their earlier treatment in the index studies. On Week 1 Day 1 of the OLE study, patients who received placebo in the index study will receive the first treatment of volanesorsen (single-dose PK), while patients who received volanesorsen in the index studies had been on volanesorsen treatment for 12 months (ISIS 304801-CS6) or 6 months (ISIS 304801-CS16), thus the PK data collected from these patients reflect steady-state PK. The maximum observed drug concentration (C_{max}) and the time taken to reach C_{max} (T_{max}) will be obtained directly from the concentration-time data. Area under the plasma concentration-time curve from time zero to 24 hours ($AUC_{0\text{-}24hr}$) will be calculated using the linear trapezoidal rule. Apparent systemic (plasma) clearance after SC administration ($CL_{0\text{-}24hr}/F_{0\text{-}24hr}$) will be calculated from $CL_{0\text{-}24hr}/F_{0\text{-}24hr}$ = Actual Dose/$AUC_{0\text{-}24hr}$. Mean

residence time (MRT) from time zero to 24 hours after the SC administration will be calculated from the equation, $MRT_{0\text{-}24hr} = AUMC_{0\text{-}24hr}/AUC_{0\text{-}24hr}$, where $AUMC_{0\text{-}24hr}$ is the area under the moment plasma concentration-time curve from time zero to 24 hours after the SC administration. Other PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist.

Plasma PK parameters will be summarized using descriptive statistics, with and without stratification by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16 and IM status. Additional details regarding the PK analysis will be described in the SAP.

Population PK, PK/PD, and covariate analysis may be performed if deemed appropriate, and results will be reported separately.

10.6.4.2 Immunogenicity Analysis

Immunogenicity (IM) results (screen positive/negative, confirmed positive/negative or not evaluable, and when applicable, titer of anti-volanesorsen antibodies) before, during, and after treatment with Study Drug (volanesorsen) (i.e., sample [anti-drug antibody] ADA status) will be listed by their prior treatment in study ISIS 304801-CS6 or ISIS 304801-CS16 and study day. Subject ADA status (positive/negative or not evaluable) for all evaluable patients, along with the study day associated with the first positive IM status emerged (T_{first}, i.e., onset of ADA development), the last positive IM status observed (T_{last}), the duration of ADA response (number of days between T_{first} and T_{last}) if appropriate, the last ADA sample collection day, and subject - peak titer if applicable, will be listed by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16 study day. Subjects with positive anti-volanesorsen antibody status may be further classified (when applicable) as being either 'persistent', 'transient', or 'not determinable', if deemed appropriate.

Additionally, the sample and subject IM incidence (number) and incidence rate (percent) will be summarized as the total number and percent of evaluated subjects with antibody negative, positive, and unknown status by their prior treatment in Study ISIS 304801-CS6 and ISIS 304801-CS16. Furthermore, onset, duration, and titer of the ADA response, if applicable, will be summarized as median, quartiles (25% and 75%), and range.

Additional details regarding the IM data analysis will be described in the SAP.

Potential relationships between immunogenicity results (e.g., IM status) and selected efficacy (e.g., % change in fasting TG from baseline at 3-, 6-, and 12-month endpoints), safety, and PK (e.g., C_{trough}) measures will be evaluated using graphical analysis and statistical analysis. These analyses will be either conducted and included in the study report, or data pooled and analyzed from all available Phase 2 and 3 studies and reported separately.

11. INVESTIGATOR'S REGULATORY OBLIGATIONS

11.1 Informed Consent

The written informed consent document should be prepared in the language(s) of the potential patient population, based on an English version provided by the Sponsor.

Before a patient's participation in the trial, the Investigator is responsible for obtaining written informed consent from the patient after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific qualification procedures or any Study Drug are administered. The patient must be given sufficient time to consider whether to participate in the study.

The acquisition of informed consent and the patient's agreement or refusal to notify his/her primary care physician should be documented in the patient's medical records and the informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion (not necessarily an Investigator). The original signed informed consent form should be retained in the Study Master File and in any other locations required by institutional policy, and a copy of the signed consent form should be provided to the patient.

11.2 Ethical Conduct of the Study

The Guidelines of the World Medical Association (WMA) Declaration of Helsinki dated October 2002 the applicable regulations and guidelines of current Good Clinical Practice (GCP) as well as the demands of national drug and data protection laws and other applicable regulatory requirements will be strictly followed.

11.3 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent form, other written patient information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by the Sponsor before recruitment of patients into the study and shipment of volanesorsen. A copy of the written approval of any other items/materials that must be approved by the Study Center or IEC/IRB must also be received by the Sponsor before recruitment of patients into the study and shipment of Study Drug. The Investigator's Brochure must be submitted to the IEC/IRB for acknowledgement.

The Investigator must submit to and, where necessary, obtain approval from the IEC/IRB, for all subsequent protocol amendments and changes to the informed consent document. The Investigator should notify the IEC/IRB of deviations from the protocol in accordance with ICH GCP Section 4.5.2. The Investigator should also notify the IEC/IRB of serious adverse events occurring at the Study Center and other adverse event reports received from the Sponsor, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study. Copies of the Investigator's reports, all IEC/IRB submissions and the IEC/IRB continuance of approval must be sent to the Sponsor.

11.4 Patient Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained. On the case report forms (CRF) or other documents submitted to the Sponsor, patients should be identified by unique initials and a patient study number only. Documents that are not for submission to the Sponsor (e.g., signed informed consent forms) should be kept in strict confidence by the Investigator.

In compliance with Federal and local regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the patient to permit named representatives to have access to his/her study-related records without violating the confidentiality of the patient.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments

Protocol amendments must be made only with the prior approval of the Sponsor. Agreement from the Investigator must be obtained for all protocol amendments and amendments to the informed consent document. The regulatory authority and IEC/IRB must be informed of all amendments and give approval for any amendments likely to affect the safety of the patients or the conduct of the trial. The Investigator **must** send a copy of the approval letter from the IEC/IRB to the Sponsor.

12.2 Study Termination

The Sponsor reserves the right to terminate the study according to the terms of the site contract. The Investigator reserves the right to terminate their participation in the study, according to the terms of the site contract. The Investigator/Sponsor should notify the IEC/IRB in writing of the trial's completion or early termination and send a copy of the notification to the Sponsor.

12.3 Study Documentation and Storage

An electronic case report form (eCRF) utilizing an Electronic Data Capture (EDC) application will be used for this study.

The Investigator should ensure that all appropriately qualified persons to whom he/she has delegated trial duties are recorded on a Sponsor-approved Delegation of Site Responsibilities Form.

Source documents are original documents, data, and records from which the patient's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, imaging, and correspondence. In this study, CRFs may not be used as source documents.

The Investigator and Study Center staffs are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation in accordance with Section 8 of the ICH Guidelines (E6), suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Elements should include:

- Patient files containing completed CRFs, informed consents, and supporting copies of source documentation

- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation and all correspondence to and from the IEC/IRB and the Sponsor
- If volanesorsen supplies are maintained at the Study Center, proof of receipt, volanesorsen Accountability Record, Return of volanesorsen for Destruction, final study volanesorsen reconciliation, and all volanesorsen-related correspondence

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

No study document should be destroyed without prior written agreement between the Sponsor or and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor.

12.4 Study Monitoring

The Sponsor representative and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the trial (e.g., CRFs and other pertinent data) provided that patient confidentiality is respected.

The Sponsor monitor is responsible for inspecting the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to patient medical records and other study-related records needed to verify the entries on the CRFs.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's Clinical Quality Assurance Department. Inspection of Study Center facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the trial conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

To ensure the quality of clinical data a clinical data management review will be performed on patient data received by the Sponsor. During this review, patient data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or Study Center notifications will be sent to the Study Center for completion and return to Sponsor.

The Principal Investigator will sign and date the indicated places on the CRF. These signatures will indicate that the principal Investigator inspected or reviewed the data on the CRF, the data queries, and the Study Center notifications, and agrees with the content.

12.5 Language

Case report forms must be completed in English. Generic names for concomitant medications should be recorded in English if possible, unless it is a combination drug, then record the trade name in English.

All written information and other material to be used by patients and investigative staff must use vocabulary and language that are clearly understood.

12.6 Compensation for Injury

The Sponsor maintains appropriate insurance coverage for clinical trials and will follow applicable local compensation laws. Patients will be treated and/or compensated for any study-related illness/injury in accordance with the information provided in the Compensation for Injury section of the Informed Consent document.

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14. APPENDICES

Appendix A Schedule of Procedures

Appendix A Schedule of Procedures

Study Period		Qual[a]	Treatment Period														Post Treatment Follow-up	
Study Week		-2 to -1	Wk 1		Wk 4	Wk 8	Month 3		Wk 19	Month 6		Wk 32	Wk 38	Wk 44	Month 12		Wk 58	Wk 65
							Wk 12	Wk 13		Wk 25	Wk 26				Wk 51	Wk 52 or ET		
Study Day		-14 to -7	1	2	22	50	78	85	127	169	176	218	260	302	351	358	400	449
Visit Window+/- Days		0	0	0	2	2	2	2	3	2	2	3	3	3	2	2	7	7
Informed Consent		X																
Outpatient Visit		X	X	X	X	X	X[h]	X	X[h]	X[h]	X	X[h]	X	X[h]	X[h]	X	X[h]	X
Inclusion/Exclusion Criteria		X																
Vital Signs + body weight (+ height on Day 1 only)		X	X		X	X		X			X		X			X		X
Physical Examination			X					X			X		X			X		X
12- lead ECG (triplicate)								X			X		X			X		X
MRI (liver/spleen)																X[i]		
Echocardiography											X[i]					X[i]		
Fundus Photography[b]		X														X[i]		
Blood Draw (Fasting)[c]	Chemistry Panel	X	X		X	X		X	X[h]		X	X[h]	X	X[h]		X	X[h]	X
	CBC with Differential	X	X		X	X		X	X[h]		X	X[h]	X	X[h]		X	X[h]	X
	Serum Lipid Panel	X	X		X	X	X[h]	X		X[h]	X		X		X[h]	X		X
	Coagulation (aPTT, PT, INR)					X		X			X		X			X		
	hsCRP, HbA1c, FPG, and de-lipidated free glycerol		X					X			X					X		X
	Sedimentation Rate		X					X			X					X		X
	Complement (C5a, Bb)		X					X			X					X		X
	Plasma PK - Volanesorsen		X[k]	X	X	X		X			X		X			X		X
	Anti-Volanesorsen Antibodies		X		X	X		X			X		X			X		X
	FSH (women only, if applicable)																	
	Serum Pregnancy Test[d]	X				X		X			X		X			X		X
	Archived Serum & Plasma Samples[e]		X			X		X			X					X		X

Appendix A Schedule of Procedures *Continued*

Study Period	Qual[a]	Treatment Period														Post Treatment Follow-up	
Study Week	-2 to -1	Wk 1		Wk 4	Wk 8	Month 3		Wk 19	Month 6		Wk 32	Wk 38	Wk 44	Month 12		Wk 58	Wk 65
						Wk 12	Wk 13		Wk 25	Wk 26				Wk 51	Wk 52 or ET		
Study Day	-14 to -7	1	2	22	50	78	85	127	169	176	218	260	302	351	358	400	449
Visit Window+/- Days	0	0	0	2	2	2	2	3	2	2	3	3	3	2	2	7	7
Urinalysis[c]	X	X[j]		X	X		X[j]	X[j,h]		X[j]	X[j,h]	X[j]	X[j,h]		X[j]	X[j,h]	X[j]
Weekly Study Drug: SC Injection		X		X	X	X	X	X	X	X	X	X	X	X	X		
Symptom Diary (weekly)	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Assessment(s)		X					X			X					X		X
Food/Drink Diary (quarterly)[f]		X					X			X					X		X
Diet/Alcohol Counseling[g]	X	X		X	X		X			X		X			X	X	X
Adverse Events	X	X		X	X		X			X		X			X		X
Concomitant Medication	X	X		X	X		X			X		X			X		X

a Qualification procedures performed (Please refer to Section 4.1)

b If possible, prior to administration of the first dose of Study Drug and repeated at Week 52 (Please refer to Section 6.2.2.2)

c Blood samples to be collected after an overnight fast of at least 10 hours. During treatment period urine and blood samples will be collected prior to Study Drug administration. Does not apply to 24-hour PK blood draw

d Females of childbearing potential only

e Serum and plasma samples will be collected and stored for follow-up exploration of laboratory findings and/or adverse events (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.) in this or subsequent clinical studies of volanesorsen

f In addition to diary, patients will be contacted at random times during the study to review their current eating and drinking habits

g To reinforce compliance to the diet and alcohol restrictions. Random diet/alcohol assessments (phone visits) will also be performed by dietician or study personnel

h To be collected by either a clinical service, or Study Center as arranged by the Study Center personnel. Approval for study procedures to be conducted by a clinical service on other outpatient visit days will require prior approval by the Sponsor.

i A ± 7 day window is allowed for MRI, echocardiography procedures and fundus photography

j Expanded urinalysis (see Appendix B)

k Full or abbreviated PK profile (see Appendix C)

Appendix B List of Laboratory Analytes

Appendix B List of Laboratory Analytes

Based on emerging data from this or future studies, additional tests not listed below may be performed on stored samples to better characterize the profile of volanesorsen or other similar oligonucleotides.

Clinical Chemistry Panel

- Sodium
- Potassium
- Chloride
- Bicarbonate
- Total protein
- Albumin
- Calcium
- Magnesium
- Phosphorus
- Glucose
- BUN
- Creatinine
- Uric Acid
- Total bilirubin
- Direct (conjugated) bilirubin
- Indirect (unconjugated) bilirubin
- ALT
- AST
- Alkaline phosphatase

Coagulation

- aPTT (sec)
- PT (sec)
- INR

Lipid Panel

- Total Cholesterol
- LDL-C
- HDL-C
- Triglycerides
- Non-HDL-C
- VLDL-C
- apoA-1
- apoB
- apoC-III

Hematology

- Red blood cells
- Hemoglobin
- Hematocrit
- MCV, MCH, MCHC
- Platelets
- White blood cells
- WBC Differential (% and absolute)
  - Neutrophils
  - Eosinophils
  - Basophils
  - Lymphocytes
  - Monocytes

Pharmacokinetics[1] & Immunogenicity

- Volanesorsen levels in plasma
- Anti-volanesorsen antibodies in plasma

Other assessments

- hsCRP
- Sedimentation Rate
- C5a, Bb
- De-lipidated free glycerol
- HbA1c, FPG

Urinalysis

- Color
- Appearance
- Specific gravity
- pH
- Protein
- Blood
- Ketones
- Urobilinogen
- Glucose
- Bilirubin
- Leukocyte esterase
- Nitrate
- Microscopic examination[2]

Additional Measures for Expanded Urinalysis

- Total protein (quantitative)
- Microalbumin
- β2-microglobulin

1 Plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, IM testing (or possibly for purposes of IM assay development and/or validation), or to assess other actions of volanesorsen with plasma constituents

2 Will be performed on abnormal findings unless otherwise specified

Appendix C Pharmacokinetic Sampling Schedule

Appendix C Pharmacokinetic Sampling Schedule

Blood samples for the determination of plasma volanesorsen concentrations will be collected prior to dosing, and at various times throughout the dosing and post-treatment follow-up period as noted in the tables below.

PK Sampling Schedule (All Patients except PK Subgroup)

Week	Wk 1	Wk 4	Wk 8	Wk 13	Wk 26	Wk 38	Wk 52	Wk 65
Study Day	D1	D22	D50	D85	D176	D260	D358	D449
Visit Window +/- Days	0	2	2	2	2	3	2	7
Time Point	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime

PK Sampling Schedule (PK Subgroup only*)

Week	Wk 1	Wk 1	Wk 4	Wk 8	Wk 13	Wk 26	Wk 38	Wk 52	Wk 65
Study Day	D1	D2	D22	D50	D85	D176	D260	D358	D449
Visit Window +/- Days	0	0	2	2	2	2	3	2	7
Time Point	Pre-dose, 1, 2, 3, 4, 6, 8, and 12 hrs post-dose	24 hrs post-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime

* Patients at selected sites will be asked to participate in the extended 24-hour PK profile beginning on Study Day 1. Participation is optional.

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

The following grading recommendations for adverse events relating to lab test abnormalities are based upon the **Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010**

Adverse Event	Mild	Moderate	Severe
Hematology			
aPTT prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage
Eosinophils increased†	650 – 1,500 cell/mm^3	1,501 - 5,000 cell/mm^3	>5,000 cell/mm^3
Fibrinogen decreased	<1.0 - 0.75 x LLN or <25% decrease from baseline	<0.75 - 0.5 x LLN or 25 - <50% decrease from baseline	<0.5 x LLN or ≥50% decrease from baseline
Hemoglobin decreased (Anemia)	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated
Hemoglobin increased	Increase in >0 - 2 g/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 g/dL above ULN or above baseline if baseline is above ULN	Increase in >4 g/dL above ULN or above baseline if baseline is above ULN
INR increased	>1 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation
Lymphocyte count decreased	<LLN - 800/mm^3; <LLN - 0.8 x 10^9/L	<800 - 500/mm^3; <0.8 - 0.5 x 10^9 /L	<500 /mm^3; <0.5 x 10^9 /L
Lymphocyte count increased	-	>4000/mm^3 - 20,000/mm^3	>20,000/mm^3
Neutrophil count decreased	<LLN - 1500/mm^3; <LLN - 1.5 x 10^9 /L	<1500 - 1000/mm^3; <1.5 - 1.0 x 10^9 /L	<1000/mm^3; <1.0 x 10^9 /L
Platelet count decreased	<LLN - 75,000/mm^3; <LLN - 75.0 x 10^9 /L	<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9 /L	<50,000/mm^3; <50.0 x 10^9 /L
White blood cell decreased	<LLN - 3000/mm^3; <LLN - 3.0 x 10^9 /L	<3000 - 2000/mm^3; <3.0 - 2.0 x 10^9 /L	<2000/mm^3; <2.0 x 10^9 /L
Chemistry			
Acidosis	pH <normal, but **>=**7.3	-	pH <7.3
Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Alkalosis	pH >normal, but ≤7.5	-	pH >7.5
Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 x ULN
Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

Adverse Event	Mild	Moderate	Severe
Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer
CD4 lymphocytes decreased	<LLN - 500/mm^3; <LLN - 0.5 x 10^9 /L	<500 - 200/mm^3; <0.5 - 0.2 x 10^9 /L	<200/mm^3; <0.2 x 10^9 /L
CPK increased*	>ULN - <6 ULN	6 - 10 x ULN	>10 x ULN
Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 x ULN
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 mg/dL; >3.1 mmol/L; Ionized calcium >1.6 mmol/L; hospitalization indicated
Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 mg/dL; >13.9 mmol/L; hospitalization indicated
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0; hospitalization indicated
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 mg/dL; >1.23 mmol/L
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 mmol/L; hospitalization indicated
Hyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 mg/dL; <1.75 mmol/L; Ionized calcium <0.9 mmol/L; hospitalization indicated
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 mg/dL; <3.0 mmol/L	<40 mg/dL (<2.2 mmol/L) AND requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions‡
Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 mmol/L; hospitalization indicated
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 mg/dL; <0.4 mmol/L
Hyponatremia	<LLN - 130 mmol/L	-	<130 mmol/L
Hypophosphatemia	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 mg/dL; <0.6 mmol/L
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

Adverse Event	Mild	Moderate	Severe
Urine			
Proteinuria Adults Children	1+ proteinuria; urinary protein <1.0 g/24 hrs -	2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs; Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Urinary protein ≥3.5 g/24 hrs; Urine P/C >1.9
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated

[†]Grading for this parameter is derived from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007

[*]Grading for this parameter is derived from the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0, Nov 2014

[‡]Modified for consistency with the ADA and Endocrine Society Guidelines (Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. Diabetes Care 2013;36:1384-95)

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ISIS 304801-CS7

The APPROACH Open Label Extension Study

Volanesorsen (ISIS 304801)

An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Original Protocol – 28 August 2015

EudraCT No: 2015-003755-21

ISIS 304801-CS7

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Confidentiality Statement

This document contains confidential information of Isis Pharmaceuticals, Inc., that must not be disclosed to anyone other than the recipient study staff and members of the independent ethics committee, institutional review board, or authorized regulatory agencies. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Isis Pharmaceuticals, Inc.

Protocol Signature Page

Protocol Number: ISIS 304801-CS7

Protocol Title: An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)

Date: 28 August 2015

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)", dated 28 August 2015, and agree to conduct the study as described herein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice (E6).

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Isis Pharmaceuticals, Inc.

Investigator's Signature

Investigator's Name *(please print)*

Date (DD Month YYYY)

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PROTOCOL SYNOPSIS

Protocol Title	An Open-Label Extension Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS)
Study Phase	3
Indication	Familial Chylomicronemia Syndrome
Study Objectives	To evaluate the safety and efficacy of extended dosing with volanesorsen (volanesorsen sodium 300 mg) in patients with FCS
Study Design	This is a multi-center, open-label extension study of ISIS 304801-CS6. All patients will receive volanesorsen 300 mg once per week for 52 weeks. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period. Following the Week 52 visit, patients will enter a 13 week post-treatment evaluation period.
Number of Patients	Up to approximately 50 patients dosed
Study Population	Inclusion Criteria: 1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law 2. Age ≥ 18 years at time of informed consent 3. Satisfactory completion of ISIS 304801-CS6 (index study) with an acceptable safety profile, per Sponsor and Investigator judgment 4. Able and willing to participate in a 65-week study 5. Satisfy one of the following: a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved), abstinent, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration b. Males: Surgically sterile, abstinent or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration Exclusion Criteria: 1. Have any new condition or worsening of existing condition which in the opinion of the Investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study 2. Unwilling to comply with lifestyle requirements for the duration of the study (Section 6.3)
Treatment Group	Volanesorsen 300 mg once per week
Study Drug Administration	Volanesorsen will be administered as subcutaneous (SC) injections.

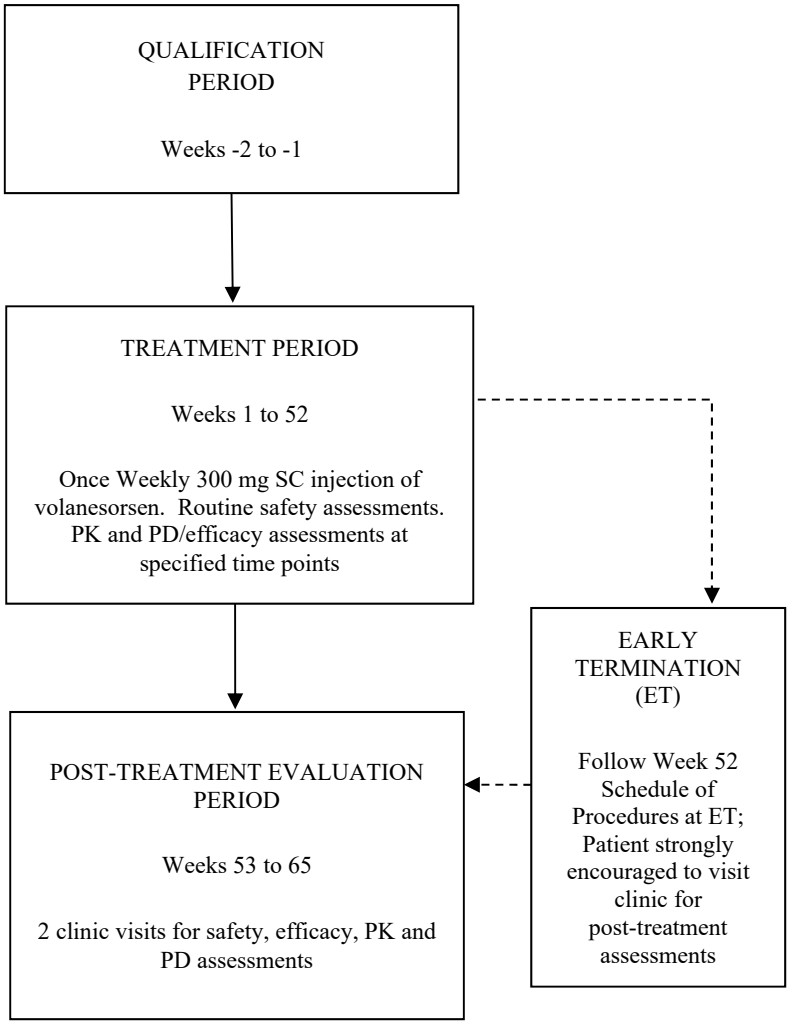
PROTOCOL SYNOPSIS *Continued*

Dose Adjustments	Dose adjustments, including dose interruptions and/or decreasing the dose frequency will be allowed for safety or tolerability after consultation with the Sponsor Medical Monitor.
Rationale for Dose and Schedule Selection	The dose of 300 mg once weekly was chosen for the double-blinded placebo-controlled Phase 3 index study (ISIS 304801-CS6) based on the pharmacodynamic and safety analysis of the Phase 2 studies which included a subset of patients with FCS. This is an extension to the ISIS 304801-CS6 study.
Study Visit Schedule and Procedures	The study for an individual patient will generally consist of the following periods: • A qualification period of up to 2 weeks (unless approved by the Sponsor) • A 52-week treatment period during which volanesorsen will be administered as a once weekly SC injection • A 13-week post-treatment evaluation period The patients, Investigators, study staff, and the Sponsor will remain blinded to lipid data through the last patient's Week 13 visit of the extension study or until results from the database lock for the index study (ISIS 304801-CS6) becomes available, whichever comes first. Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), adverse events (AE), concomitant medication/procedure information, lipid panel, volanesorsen plasma concentrations, immunogenicity (IM) testing, liver/spleen magnetic resonance imaging (MRI), ECGs, echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Dietary counseling will be repeated at intervals throughout the treatment and follow-up period and a daily food/drink diary will be completed for the week prior to each quarterly visit by each patient. Following the Week 52 visit, patients will enter the 13-week post-treatment evaluation period.
Safety and Tolerability Evaluations	Overall safety and tolerability of volanesorsen will be assessed by determining the incidence and severity of adverse and serious adverse events (including independently adjudicated events of acute pancreatitis and MACE), withdrawals due to adverse events, and changes in laboratory and other safety parameters.
Planned Analyses	Safety Endpoints: • Adverse events including adjudicated events of acute pancreatitis and MACE • Vital signs and weight • Physical examinations • Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis) • Echocardiography • Electrocardiograms (ECGs) • Use of concomitant medications • MRIs

PROTOCOL SYNOPSIS *Continued*

Planned Analyses *Continued*	Efficacy Endpoints: • Percent change and absolute change from baseline in fasting TG • Frequency and severity of patient reported abdominal pain during the treatment period • Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-high-density lipoprotein-cholesterol (non-HDL-C), apolipoprotein B [apoB], high-density lipoprotein-cholesterol (HDL-C), apolipoprotein A-1 [apoA-1], very-low-density lipoprotein-cholesterol (VLDL-C), and LDL-C • Percent change from baseline in fasting total apolipoprotein C-III (apoC-III) • Quality of Life questionnaires (EQ-5D, SF-36) • Adjudicated acute pancreatitis event rate
Pharmacokinetic Evaluations	Plasma samples will be taken from all patients for the measurement of volanesorsen as follows: trough levels (pre-dose) throughout treatment and post-treatment levels during the post-treatment follow-up period. In a subset of patients, more frequent assessment of plasma concentrations of volanesorsen will be performed to determine volanesorsen pharmacokinetic parameters. Plasma sample collection time points are detailed in Appendix A and Appendix C.
Statistical Considerations	No sample size calculations were performed as this is an extension study to the double-blind placebo controlled ISIS 304801-CS6 study.
Sponsor	Isis Pharmaceuticals, Inc.
Collaborator	Akcea Therapeutics

STUDY DESIGN AND TREATMENT SCHEMA



STUDY GLOSSARY

Abbreviation/Acronym	Definition
ADA	anti-drug antibody
AE	adverse Event
ALP	alkaline Phosphatase
ALT	alanine Aminotransferase
ANA	antinuclear Antibody
apoA-1	apolipoprotein A-1
apoB	apolipoprotein B
apoC-III	apolipoprotein C-III
apoE	apolipoprotein E
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
CBC	complete blood count
C_{max}	maximum observed drug concentration
CRF	case report form
DNA	deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
ET	early termination
FAS	full analysis set
FCS	Familial Chylomicronemia Syndrome
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
GPIHBP1	Glycosylphosphatidylinositol-anchored HDL-binding Protein 1
HAPI	Heritability and Phenotype Intervention
HbA1c	Glycated Hemoglobin
HDL	High-Density Lipoprotein
HDL-C	High-Density Lipoprotein-Cholesterol
hsCRP	High-sensitivity C-reactive protein
ICH	International Conference on Harmonization
IDL	Intermediate density lipoprotein
IEC	Independent Ethics Committee
IM	immunogenicity
Index Study	ISIS 304801-CS6

INR	International Normalized Ratio
IRB	Institutional Review Board
IXRS	Interactive Voice/Web-Response System
LDL	Low-Density Lipoprotein
LDL-C	Low-Density Lipoprotein-Cholesterol
LMF1	Lipase Maturation Factor 1
LPL	Lipoprotein Lipase
MACE	Major Acute Cardiovascular Event
MOE	2′-*O*-(2-methoxyethyl)
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NCS	not clinically significant
NOAEL	No-Observed-Adverse-Effect Level
non-HDL-C	Non-High-Density Lipoprotein-Cholesterol
OLE	Open Label Extension
OTC	over the counter
PFS	prefilled syringe
PD	pharmacodynamic
PK	pharmacokinetic
PPS	per protocol set
PT	prothrombin time
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SUSAR	suspected unexpected serious adverse reaction
T2DM	type 2 diabetes mellitus
T_{max}	time to maximal concentration
TG	triglycerides
Treatment emergent	occurring after first dose of study drug
TRL	Triglyceride-Rich Lipoproteins
ULN	upper limit of normal
VLDL	Very-Low-Density Lipoprotein
VLDL-C	Very-Low-Density Lipoprotein-Cholesterol
VLDL-TG	Lipoprotein-Triglyceride
WMA	World Medical Association

1. OBJECTIVES

The objective of the study is to evaluate the safety and efficacy of extended dosing with volanesorsen in patients with familial chylomicronemia syndrome.

2. BACKGROUND AND RATIONALE

2.1 Overview of Disease

Familial Chylomicronemia Syndrome (FCS) is an inherited disease characterized by severe hypertriglyceridemia and chylomicronemia, and risk or history of pancreatitis. It is a rare autosomal recessive disease that can be diagnosed either in childhood or adulthood.

Fasting plasma triglyceride (TG) levels in FCS patients are typically 10-fold to 100-fold above normal (1,500 to 15,000 mg/dL), despite extreme dietary fat restriction (20 g or approximately 15-20% of daily calorie intake) (Brunzell 1999-2011). Patients with FCS often present in infancy or childhood with frequent and severe abdominal pain, repetitive colicky pain, repeated episodes of potentially fatal acute pancreatitis, and failure to thrive (Brunzell 1999-2011; Tremblay et al. 2011). Physical examination frequently reveals eruptive xanthomas, lipemia retinalis and hepatosplenomegaly, and plasma from patients appears lactescent, interfering with determination of other laboratory parameters (Tremblay et al. 2011).

Patients with fasting triglyceride levels > 10 mmol/l probably have a component of chylomicronemia. Clinical diagnosis would include evidence of clinical features of chylomicronemia syndrome and secondary causes such as uncontrolled type 1 or type 2 diabetes mellitus (T2DM), hypothyroidism, poor diet, alcohol use, nephrotic syndrome or use of associated medications should be ruled out. The diagnosis of FCS may be made more specifically by genotyping or confirmation of very low or absent lipoprotein lipase (LPL) enzyme activity in post heparin plasma (Brunzell 1999-2011).

Patients with FCS carry a heavy burden of medical complications, the most serious, as described above, being an extreme risk of recurrent and potentially fatal pancreatitis. Due to the recurrent episodes of acute pancreatitis, these patients may also develop chronic pancreatitis and signs of exocrine or endocrine pancreatic insufficiency, including diabetes mellitus (Gaudet et al. 2013). While the pathophysiology underlying chylomicron-related pancreatitis has not been completely elucidated, one hypothesis is that large chylomicrons lodged in pancreatic capillaries are exposed to pancreatic lipase, with the subsequent release of free fatty acids through the hydrolysis of chylomicron-associated TGs. High concentrations of free fatty acids are thought to damage pancreatic cells leading to emergent pancreatitis (Yang et al. 2009; Berglund et al. 2012).

The etiology of extreme hypertriglyceridemia in FCS is considered to be ineffective triglyceride clearance, due to an extremely low level of LPL activity. LPL normally functions to hydrolyze triglycerides (TG) in chylomicrons along the luminal surface of capillaries, mainly in heart, skeletal muscle, and adipose tissue, promoting triglyceride clearance from the circulation. LPL is regulated by a number of key genes, and loss-of-function mutations in one of these genes, or the LPL gene itself, results in FCS (Surendran et al. 2012). In addition to loss of function mutations, null mutations, and nonsense mutations in the LPL gene, other genes currently identified in FCS patients, and known to directly influence LPL activity include: apolipoprotein C-II (APOC2) a cofactor for LPL (Schuster et al. 2011); apolipoprotein A-V

(APOA5) an enhancer of LPL activity (Schaap et al. 2004); lipase maturation Factor 1 (LMF1), a transmembrane protein involved in LPL maturation (Doolittle et al. 2009); glycosylphosphatidylinositol-anchored HDL-binding protein 1 (GPIHBP1), a capillary endothelial cell protein that provides a platform for LPL-mediated processing of chylomicrons (Beigneux et al. 2007).

2.2 Therapeutic Rationale

Apolipoprotein C-III (ApoC-III), a key regulator of plasma triglyceride levels, is a 79 amino acid glycoprotein synthesized principally in the liver (Ooi et al. 2008; Figure 1). ApoC-III is a major regulator of lipoprotein metabolism and plays a pivotal role in regulating plasma TG levels (Chan et al. 2008). It is a component of triglyceride-rich lipoproteins (TRLs) and a potent inhibitor of LPL (Lemieux et al. 2003). At higher concentrations apoC-III also inhibits hepatic lipase activity (Kinnunen and Ehnolm 1976), an enzyme which plays an important role in the conversion of dense very-low-density lipoprotein (VLDL) to intermediate density lipoprotein (IDL) and to LDL (Mendivil et al. 2010), as well as in the remodeling of HDL (Brown et al. 2010). In addition, increased apoC-III content adversely affects apoE-mediated hepatic uptake of TG-rich remnants (Mann et al. 1997). Thus, elevated plasma apoC-III levels are associated with impaired hydrolysis and retarded clearance of TG-rich particles, resulting in the accumulation of lipoprotein-triglyceride (VLDL-TG) and chylomicrons in plasma and the development of hypertriglyceridemia (Ito et al. 1990).

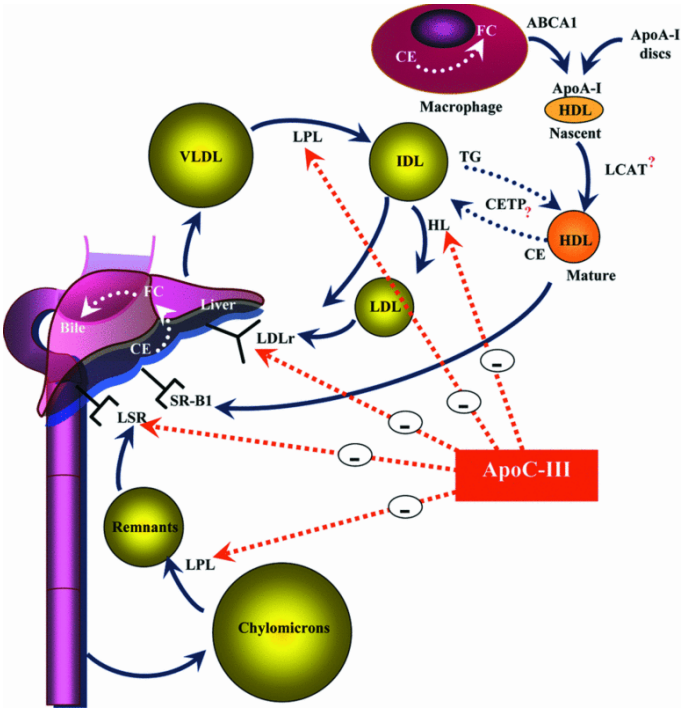


Figure 1 ApoC-III Regulates Lipoprotein Metabolism by Multiple Mechanisms

From Ooi et al. 2008; ABCA1 = ATP-binding cassette A1, apo = apolipoprotein, CE = cholesterol ester, CETP = cholesterol ester transfer protein, FC = free cholesterol, HDL = high-density lipoprotein, HL = hepatic lipase, IDL = intermediate-density lipoprotein, LCAT = lecithin cholesterol acyltransferase, LDL = low-density lipoprotein, LDLr = LDL receptor, LPL = lipoprotein lipase, LSR = lipolysis-stimulated receptor, SR-B1 = scavenger receptor B-1, TG = triglyceride, VLDL = very low-density lipoprotein.

Mechanistically, FCS is primarily a consequence of ineffective clearance of TRL. ApoC-III is a prominent component of TRL (e.g., VLDL and chylomicrons). In addition to its role in inhibiting LPL, apoC-III inhibits TRL remnant (TG-depleted remnant lipoprotein) uptake by hepatic lipoprotein receptors by steric inhibition of the interaction of apoE with these receptors.

Human genetic data have demonstrated positive phenotypic associations with loss (e.g., null or nonsense mutations) and negative effects with gain of function mutations (Atzmon et al. 2006; Pollin et al. 2008; Petersen et al. 2010). A novel nonsense mutation in the apoC-III gene was identified in the heritability and phenotype intervention (HAPI) heart study in Old Order Amish that results in lower plasma apoC-III and TG levels and lower LDL-C, increased HDL-C and reduced atherosclerosis (Pollin et al. 2008). In another study involving a group of 214 Ashkenazi Jews of advanced age (had passed or nearly reached 100 years of age), genotype analysis revealed a polymorphism in the apoC-III gene (APOC3-641CC genotype) with a clear pattern of age-dependent frequency that was associated with significantly lower levels of apoC-III protein, a favorable lipoprotein profile and increased longevity (Atzmon et al. 2006). In contrast to the Amish and Ashkenazi apoC-III polymorphisms associated with lower plasma TG, apoC-III polymorphisms associated with higher plasma TG have also been recently described (Petersen et al. 2010). In a cohort of lean (mean body mass index [BMI] = 24.7 ± 3.6 kg/m^2) Asian Indians, carriers of apoC-III variant alleles (C-482T, T-455C, or both) were noted to have significantly higher plasma apoC-III and TG levels, and decreased ability to clear postprandial plasma TG from the circulation. Taken together, the available data strongly support the development of a therapy that reduces plasma apoC-III levels in order to reduce the very high circulating triglyceride and chylomicron levels that are accompanied by increasing risk for acute pancreatitis.

Given the profound reductions in TGs observed with volanesorsen treatment in FCS patients who have no detectable LPL activity (See Section 2.3.4), and the mechanistic data available to date on apoC-III function, potential mechanisms that explain how apoC-III inhibition results in triglyceride reduction in FCS patients include: (1) enhancing the very small residual amounts of LPL activity that these patients may have, below the limit of detection of the assay in many cases (2) potentially enhanced activity of other lipases also involved in the metabolism and breakdown of TGs, such as hepatic lipase or endothelial lipase (Kinnunen and Ehnolm 1976), and (3) apoC-III interaction with Apolipoprotein E (apoE), an important factor in liver reuptake of lipid particles by blocking apoE-mediated uptake of lipid particles in the liver (Breyer et al. 1999), and therefore, reducing apoC-III might enhance apoE-mediated uptake of lipid particles. Volanesorsen-mediated reduction of apoC-III could be contributing to one or all of these mechanisms resulting in the observed potent and sustained reductions in TG.

Through a novel apoC-III lowering mechanism of action, volanesorsen may provide the potential to manage triglyceride levels in FCS patients.

2.3 Volanesorsen

2.3.1 Mechanism of Action

Volanesorsen is a second-generation antisense oligonucleotide (ASO) drug targeted to human apoC-III. It is complementary to a region within the 3′ untranslated region of the apoC-III messenger ribonucleic acid (mRNA) and binds to the mRNA by Watson and Crick base pairing.

The hybridization (binding) of volanesorsen to the cognate mRNA, results in the RNase H1-mediated degradation of the apoC-III mRNA, thus preventing production of the apoC-III protein. Maximal antisense-mediated reduction of target mRNA levels is typically greater than 90% of control levels in sensitive tissues (Crooke and Bennett 1996; Zhang et al. 2010). Furthermore, reduction in target mRNA levels using this approach correlates directly with a subsequent reduction in target protein levels.

2.3.2 Chemistry

Chemically, volanesorsen is a synthetic oligomer of 20 nucleotides (i.e., a 20-mer) that are connected sequentially by phosphorothioate linkages. The nucleotide sequence of volanesorsen (Figure 2) is complementary to a 20-nucleotide stretch within the 3′ untranslated region of the apoC-III mRNA transcript at base position 489-508. Structurally, the oligonucleotide has 3 regions. Two (2) of them, the 5 nucleotides at the 5′ end and the 5 nucleotides at the 3′ end, are composed of 2′-*O*-(2-methoxyethyl) (MOE)-modified ribonucleotides. These MOE-modified nucleotides confer (1) increased affinity to the target mRNA (Altmann et al. 1996; McKay et al. 1999), (2) increased resistance to exonucleases and endonucleases (thereby increasing stability in tissue) (Geary et al. 2003), and (3) amelioration of some of the high dose toxicities thereby resulting in an improved safety profile compared to first generation antisense drugs containing phosphorothioate modified oligodeoxynucleotides (DNA) (Henry et al. 2000). The third region, the central portion of the oligonucleotide, is composed of 10 oligodeoxynucleotides. This chimeric design is called a MOE-Gapmer, and volanesorsen employs this chimeric structure to enable use of the RNase H1-mechanism for antisense activity. This is because while the 2′-MOE modification confers increased stability and affinity, it does not support RNase H1 catalysis of RNA hybridized to 2′-MOE-modified nucleotides (McKay et al. 1999). This is caused by conformational changes induced in the heteroduplex by 2′-alkoxy:RNA hybrids that are not recognized by RNase H1 enzymes (Inoue et al. 1987; Monia et al. 1993). By limiting the 2′-MOE modification to nucleotides flanking the phosphorothioate oligodeoxynucleotide core, the beneficial attributes of the 2′-MOE chemistry are preserved while also retaining RNase H1 recognition.

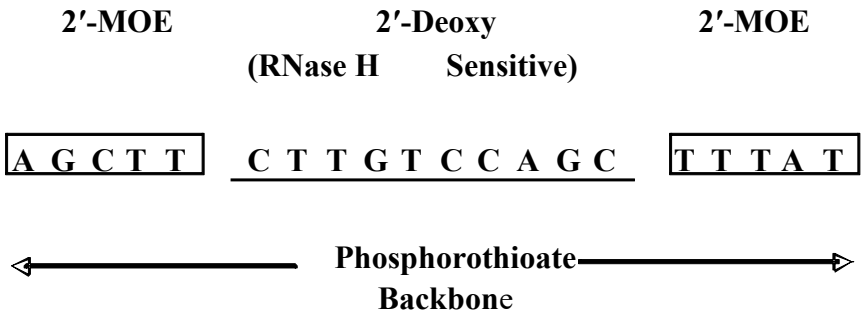


Figure 2 Design of Chimeric 2′-MOE Phosphorothioate Oligonucleotides (MOE-Gapmer). The sequence of volanesorsen is shown

2.3.3 Preclinical Experience

Inhibition of apoC-III using volanesorsen has been shown to potently reduce hepatic apoC-III mRNA as well as plasma apoC-III protein and TG in a dose- and time-dependent fashion in several species, including human apoC-III transgenic mice, and other rodent and monkey models. Treatment with volanesorsen also resulted in reduced VLDL and chylomicron TG and reduced postprandial TG in hypertriglyceridemic monkeys (Graham et al. 2013).

The pharmacokinetics (PK) and toxicity of volanesorsen have been assessed in mice, rats, and cynomolgus monkeys. General toxicity studies with volanesorsen for up to 39 weeks of treatment followed by up to a 20-week recovery period are complete. The preclinical toxicology program for volanesorsen consists of single dose safety pharmacology studies in the monkey (cardiovascular) and mouse (neurobehavioral and pulmonary assessment studies), *in vitro* and *in vivo* genetic toxicity assessment, repeat dose fertility and/or developmental reproductive toxicology studies in the mouse and rabbit and evaluation in the *in vitro* human Ether-á-go-go-related gene (hERG) assay.

Volanesorsen treatment-related findings in mice and monkeys were generally consistent with those expected for the 2′-MOE-class of ASOs. Treatment-related findings included effects consistent with drug accumulation in tissues in rodents and monkeys, species-dependent proinflammatory response in rodents and monkeys and complement activation and reductions in platelet counts in the monkey. In the mouse and monkey general toxicity studies, reduction of hepatic apoC-III mRNA (> 75%) was not associated with any findings that could be considered related to the pharmacologic inhibition of apoC-III for up to 39 weeks of treatment.

The long-term, chronic toxicology studies in rodents with volanesorsen produced a significant proinflammatory response that led to subsequent effects on the heart at high doses. The rodent species are most sensitive to the proinflammatory effects of antisense molecules. Importantly, these effects on the heart were not observed in the monkey chronic toxicity studies even at the highest doses tested where drug exposure was higher than that in rodents.

Because these changes were not observed in monkeys, the findings in the heart are considered to be rodent-specific and not relevant to humans. Nevertheless, such effects will be monitored by measurement of echocardiograms that will be included in this clinical study.

Volanesorsen caused no untoward effects in safety pharmacology studies (*in vitro* and *in vivo*) and was non-genotoxic (*in vitro* and *in vivo*). Volanesorsen had no effects on fertility or embryo/fetal development in the mouse or rabbit reproductive toxicity studies. In these studies, volanesorsen was detected in placental tissue but not in fetal tissue indicating that little, if any, drug was able to cross the placenta to reach the fetus. Reduction of apoC-III mRNA (64% in males and 47% in females) also did not affect fertility or cause untoward effects on embryo/fetal development in mice.

Detailed information concerning the preclinical studies conducted with volanesorsen can be found in the volanesorsen Investigator's Brochure.

2.3.4 Clinical Experience

Detailed information concerning the clinical studies conducted with volanesorsen can be found in the volanesorsen Investigator's Brochure. A summary is included below.

Volanesorsen has been evaluated in one Phase 1 study and two Phase 2 studies, all double blinded and placebo controlled. The total exposures comprise 99 patients and healthy volunteers administered volanesorsen from 50 to 400 mg subcutaneously up to 3 months (compared to 37 administered placebo).

All clinical trials of volanesorsen have shown large and clinically meaningful reductions in fasting plasma apoC-III and TG (~80% and 70%, respectively, mean reduction from baseline with 300 mg dose) with a very high degree of consistency of response between the different patient groups. This includes healthy volunteers, patients with moderate to severe hypertriglyceridemia not on background TG-lowering therapy, patients with moderate to severe hypertriglyceridemia on a background stable fibrate therapy (Gaudet et al. 2015), patients with FCS, and patients with T2DM.

In a Phase 2 study, three patients with FCS were treated with 300 mg/wk volanesorsen in an open label fashion. These patients had a mean baseline fasting TG level of 1,844 mg/dL and all three patients achieved TG levels below or close to 500 mg/dL during the dosing period out to Day 92 (Figure 3). Two (2) of the FCS patients had an absolute reduction in fasting TG in excess of 1,500 mg/dL (Gaudet et al. 2014).

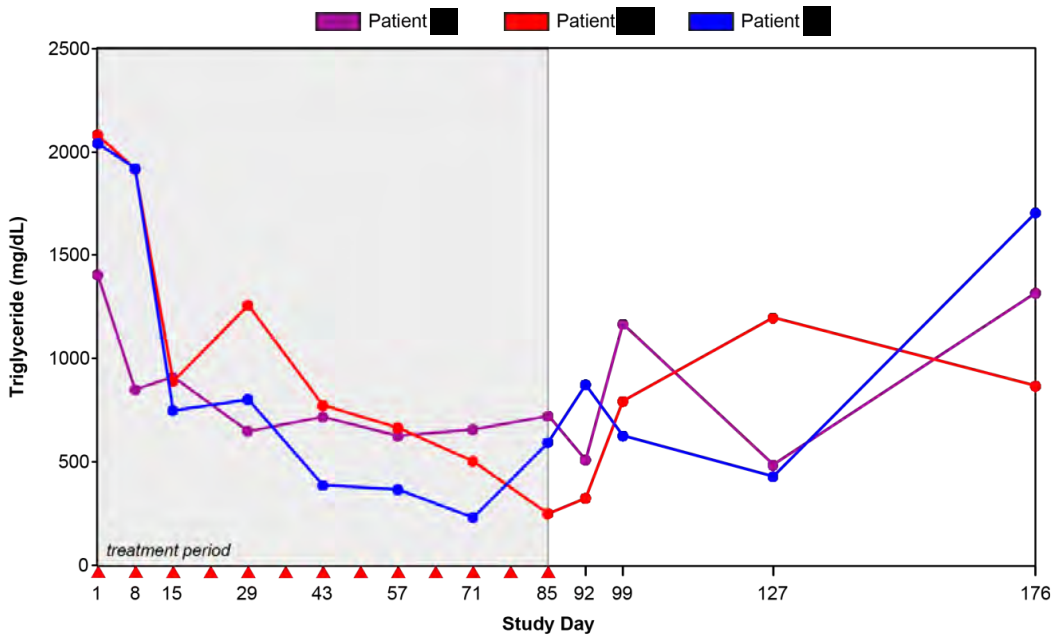


Figure 3 Fasting Triglycerides in Patients with FCS Treated with Volanesorsen

In clinical studies conducted to date volanesorsen has been well tolerated and has shown a favorable safety profile. There has been no clinical or laboratory evidence of drug-drug interactions.

To date, there have been no volanesorsen associated laboratory abnormalities suggestive of an effect on the renal (serum creatinine, proteinuria) or hepatic systems (alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin) despite many patients in the Phase 2 clinical trials receiving concomitant medications that are known to be associated with elevations in hepatic enzymes, such as fibrates and statins. In Phase 2 studies, there was a mild decrease of platelet count associated with volanesorsen administration that recovered in the post-treatment period and was not associated with platelet-related adverse events (AEs).

The most frequently observed AEs with volanesorsen were local reactions at the injection site. Local cutaneous reactions at the injection site defined as those events presenting as either pain, tenderness, erythema, pruritus or swelling occurring on the day of injection and persisting for at least 2 days were infrequent (~15% of injections), were almost always mild, resolved spontaneously, were non-progressive, and were not associated with systemic sequelae.

2.4 Rationale for Dose and Schedule of Administration

The dose and schedule selected for this study is 300 mg per week for 52 weeks. The dose of 300 mg per week is supported by both the cumulative nonclinical data available to date and the Phase 2 clinical data. In nonclinical studies, volanesorsen treatment-related effects in rodents and monkeys were consistent with drug accumulation in tissues and also include species-specific proinflammatory responses. In the monkey, the No-Observed-Adverse-Effect Level (NOAEL) was defined by the cumulative clinical pathology results and histopathology data which provide an adequate clinical margin. No nonclinical findings were considered to be related to the pharmacologic inhibition of apoC-III.

The safety data to date suggest that volanesorsen has been well tolerated at dose levels up to 300 mg in patients with high triglycerides (including type 2 diabetes patients and administration in combination with fibrates and statins) with the most common AEs being local to the injection site and predominantly mild. A pooled analysis of safety for the Phase 2 studies did not demonstrate any clear difference in safety or tolerability between the different doses tested (100 mg, 200 mg, and 300 mg per week for 13 weeks).

Analysis of the cohorts in which volanesorsen was studied at different doses demonstrates dose-dependent pharmacology with respect to pharmacodynamic (PD) effect on the target, apoC-III, with a clear difference in the TG-lowering effect between the different doses in the 100 mg to 300 mg dose range as compared to placebo.

In addition to the nonclinical and clinical experience of volanesorsen, the dose and schedule of administration is supported by the preclinical and clinical safety experience of several other 2′-MOE-modified ASOs that have been safely administered intravenously and subcutaneously in multiple clinical studies at doses up to 1000 mg and for treatment durations that exceed 24 months (Santos et al. 2015).

3. EXPERIMENTAL PLAN

3.1 Study Design

This is an open-label extension to the Phase 3 study of volanesorsen in patients with FCS (ISIS 304801-CS6). Up to approximately 50 patients will receive 300 mg once weekly volanesorsen for 52 weeks.

Following the Week 52 visit, patients enter a 13-week post-treatment evaluation period.

3.2 Number of Study Centers

This study will be conducted at multiple centers worldwide.

3.3 Number of Patients

Up to approximately 50 patients will be dosed.

3.4 Overall Study Duration and Follow-up

The Study will consist of the following periods:

- A qualification period of up to 2 weeks (unless approved by the Sponsor)
- A 52-week treatment period during which volanesorsen will be administered as a once weekly SC injection
- A 13-week post-treatment evaluation period

Please refer to the Schedule of Procedures in Appendix A.

3.4.1 Qualification

A period of up to 2 weeks is given to complete qualification assessments outlined in the Schedule of Procedures (Appendix A).

3.4.2 Treatment

The treatment period is 52 weeks. Eligible patients will report to the Study Center for assessments at specified intervals throughout the 52-week treatment period as detailed in the Schedule or Procedures (Appendix A). During the treatment period, volanesorsen is administered by SC injection once weekly.

3.4.3 Post-Treatment

The post-treatment evaluation period is 13 weeks and consists of two Study Center visits on Weeks 58 and 65.

3.5 End of Study

The end of study is last patient, last visit.

3.6 Data and Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) will review (as needed) safety, tolerability and efficacy data collected on volanesorsen during this study. Based on its ongoing assessment of

the safety and tolerability of volanesorsen, the DSMB will provide recommendations to the Sponsor for modifying, stopping or continuing the study as planned. Details on the safety assessments, frequency of review and meeting schedules are outlined in the DSMB Charter and/or the statistical analysis plan (SAP).

4. PATIENT ENROLLMENT

4.1 Qualification

Before patients may be enrolled into the study, the Sponsor requires a copy of the Study Center's written independent ethics committee/institutional review board (IEC/IRB) approval of the protocol, informed consent form, and all other patient information.

Final assessments from the index study may be used for qualification as long as they were conducted within 4 weeks of the qualification period. Patients or their legally acceptable representatives must sign the consent form before any study-specific procedures or evaluations related to this open label study are performed. During the qualification period, the eligibility of the patient to continue in the extension study will be determined. A period of up to 2 weeks after completion of the index study (unless approved by the Sponsor) is given to complete qualification. Qualified patients will retain the unique patient identification number that was assigned to them during the index study. The patient identification number will be used to identify the patient throughout the extension trial and must be used on all study documentation related to that patient. The patient identification number must remain constant throughout the extension trial.

4.2 Enrollment

Patients will be enrolled after all qualification assessments have been completed and after the Investigator has verified that they are eligible per criteria in Sections 5.1 and 5.2. No patient may begin treatment prior to enrollment.

Eligible patients will be enrolled using an Interactive Voice/Web-Response System (IXRS).

5. PATIENT ELIGIBILITY

To be eligible to participate in this study candidates must meet the following eligibility criteria within 2 weeks of Study Day 1, or at the time point specified in the individual eligibility criterion listed.

5.1 Inclusion Criteria

1. Must give written informed consent to participate in the study (signed and dated) and any authorizations required by law
2. Age ≥ 18 years at time of informed consent
3. Satisfactory completion of ISIS 304801-CS6 (index study) with an acceptable safety profile, per Sponsor and Investigator judgment
4. Able and willing to participate in a 65-week study

5. Satisfy one of the following:
    a. Females: Non-pregnant and non-lactating; surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved), abstinent, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration.
    b. Males: Surgically sterile, abstinent or if engaged in sexual relations with a female of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until 13 weeks after the last dose of Study Drug administration.

5.2 Exclusion Criteria

1. Have any new condition or worsening of existing condition which in the opinion of the Investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study.
2. Unwilling to comply with lifestyle requirements for the duration of the study (Section 6.3).

6. STUDY PROCEDURES

6.1 Study Schedule

All required study procedures are outlined in Appendices A, B, C, and D.

6.1.1 Qualification

Before any study-specific procedures or evaluations are initiated, patients must sign and date the informed consent form. A 2-week period is given after the index study to complete the qualification assessments. The qualification assessments will be performed at Week -2 to -1, ideally after patient eligibility has been determined, and on Study Day 1. Abnormal results may be retested for review by the Study Medical Monitor for eligibility purposes. Final assessments from the index study may be used for qualification as long as they were conducted within 4 weeks of the qualification period.

6.1.2 Treatment Period

The patients, Investigators, study staff, and the Sponsor will remain blinded to lipid data through the last patient's Week 13 visit of the index study or until results from database lock for the index study becomes available, whichever comes first.

During the treatment period, patients will report to the study center for clinic visits a minimum of 10 times during Weeks 1-52 (see Schedule of Procedures in Appendix A). Study Drug will be administered once weekly (Section 8.1). Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), AEs,

concomitant medication/procedure information, lipid panel, volanesorsen plasma concentrations, immunogenicity (IM) testing, liver/spleen MRI, ECGs, echocardiograms and quality of life assessments will be performed according to the schedule of procedures in Appendix A. Adverse events at the injection site should be collected as adverse events. Dietary counseling will be reinforced at intervals throughout the treatment and follow-up period and all patients will complete a daily food diary for one week prior to their quarterly visit. All blood and urine samples should be collected prior to volanesorsen administration. Blood sampling for lipid panels at Weeks 12, 25 and 51 may be conducted by a home healthcare nurse if more convenient for the patient. Patients must be fasted prior to drawing all blood samples and samples drawn locally must be sent to the central laboratory for analysis. Every effort should be made to ensure the previous week's dose is given 7 days prior to a scheduled clinic visit. Dosing instructions and training will be provided to the patient where applicable.

All visits have a visit window of at least ± 2 days. All reasonable attempts should be made to ensure compliance with the visit schedule as outlined in Appendix A. However, in the event that a visit does not occur or is delayed, all subsequent visits should be calculated based on the time elapsed since Day 1 rather than from the date of the previous visit.

6.1.3 Pharmacokinetic (PK) Subgroup

A subgroup of patients will participate in an extended PK collection. Patients in this subgroup will have more frequent PK sampling over a 24-hour period following the first dose on Study Day 1 in order to evaluate the plasma PK parameters of volanesorsen. Patients in this subgroup will have an additional visit to the clinic on Day 2 to collect a 24-hour post-dose blood draw after dosing on Day 1. The detailed PK sampling schedules are outlined in Appendix C.

Participation in the PK subgroup is optional for sites and patients, and consent may be withdrawn for the subgroup-specific procedures (e.g., multiple blood draws for PK) without being withdrawn from the study. If a patient withdraws consent from the subgroup procedures, he/she should remain on study and continue to follow all the non-subgroup assessments and procedures as outlined in Appendix A.

6.1.4 Post-Treatment Period

After completion of the Week 52 visit assessments, patients will enter the 13-week post-treatment evaluation period. This period consists of two Study Center visits on Weeks 58 and 65 as outlined in the Schedule of Procedures in Appendix A.

6.2 Additional Study Assessments

6.2.1 Laboratory Assessments

Laboratory analyte samples will be collected throughout the study.

A list of these analytes is contained in Appendix B.

6.2.2 Physical Exams and Vital Signs

Physical exams and vital signs will be performed as indicated in the Schedule of Procedures (Appendix A). Vital signs should include weight, blood pressure, pulse rate, respiratory rate and body temperature. Blood pressure and pulse rate will be recorded after the patient has been in a

sitting position for at least 5 minutes. Semi-supine systolic and diastolic blood pressure should always be measured on the same arm (preferentially on the left arm). Height will be measured at the Day 1 visit.

6.2.3 Echocardiography

Echocardiography for assessment of left and right ventricular function and mitral and aortic valve function will be conducted at Week 26 and Week 52 in all patients. For the purpose of assessment of treatment emergent changes, all echocardiograms will be evaluated on an ongoing basis by an independent central reader. Results will be provided to the DSMB for their review.

6.2.4 ECG

The ECG will be recorded after the patient has been resting in a supine position for at least 5 minutes. ECGs will be performed in triplicate at Week 13, Week 26, Week 38, Week 52, and Week 65.

6.2.5 MRI

MRI of the liver and spleen will be conducted at Week 52 for all patients for whom MRI is not contraindicated, e.g., patients having metal implants.

MRIs will be conducted using standardized procedures and settings. MRIs will be read by an independent central reader to assess liver fat and liver and spleen size**.**

6.2.6 Quality of Life Assessments

All patients will complete Quality of Life Questionnaires (EQ-5D and SF-36) at Week 13, Week 26 and Week 52.

6.2.7 Disease Symptom Diary

All patients will complete a symptom questionnaire once a week starting at the beginning of the qualification period and continuing to the end of the post-treatment follow-up period.

6.2.8 Diet Monitoring

All patients will be required to maintain a 7-day food diary at Week 1, Week 13, Week 26, and Week 52. Inquiries from a dietitian as to how each patient is maintaining their diet will be conducted randomly during the treatment and post treatment follow-up periods. Counseling will also be provided at home visits.

6.2.9 Family History

Family history of hypertriglyceridemia and pancreatitis will be collected for each patient.

6.3 Restriction on the Lifestyle of Patients

6.3.1 Contraception Requirements

All male patients and women of childbearing potential must refrain from sperm/egg donation and practice effective contraception from the time of signing the informed consent form until at least 13 weeks after their last dose of study treatment.

Male patients must also encourage their female partner to use effective contraception from the time of signing the informed consent until 13 weeks after the subject's last dose of study treatment.

For the purposes of this Study, women of childbearing potential are defined as any female who has experienced menarche, and who does not meet one of the following conditions:

- Postmenopausal: 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved
- 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Post hysterectomy

For the purposes of the study, effective contraception is defined as follows:

For male patients:

- Effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the use of condoms together with spermicidal foam/gel/film/ cream/suppository. Male patients must also encourage their female partner to use effective contraception from the time of signing the informed consent until 3 months after the patient's last dose of study treatment. Effective contraceptive for the female partner includes: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or barrier methods (female condom*, diaphragm, sponge, cervical cap) together with spermicidal foam/gel/film/cream/suppository. Male patients with partners that are pregnant must use condoms to ensure that the fetus is not exposed to the study drug.

For female patients:

- Using 1 or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or any 2 barrier methods (a combination of male or female condom* with diaphragm, sponge, or cervical cap) together with spermicidal foam/gel/film/cream/suppository.

*Note: A female condom and a male condom should not be used together as friction between the two can result in either product failing.

6.3.2 Other Requirements

All patients will be required to fast for at least 10 hours before visits requiring fasted blood sampling.

All patients will be encouraged to follow a diet comprising ≤ 20 g fat per day during the study.

Alcohol should not be consumed during the study.

All patients will be given an instruction card that must be presented to the treating physician if a suspected case of pancreatitis occurs. The card will explain that the patient is in a clinical trial and that serum lipase and/or amylase measures should be done in order to adjudicate the event, based on Atlanta Classification (Banks et al. 2013). If serum or amylase activity is less than 3 x upper limit of normal (ULN), imaging, preferably contrast-enhanced computed tomography, should be considered to confirm the diagnosis of acute pancreatitis per the Atlanta Criteria.

7. STUDY DRUG

7.1 Volanesorsen Description

Volanesorsen drug product (ISIS 304801) characteristics are listed in Table 1.

Volanesorsen (ISIS 304801) is contained in glass prefilled syringes (PFS). Volanesorsen and its storage and preparation instructions will be provided by the Sponsor or designee. Volanesorsen must be stored securely at 2° to 8° C and be protected from light.

Table 1 Volanesorsen (ISIS 304801) Characteristics

Strength	200 mg/mL
Volume/Formulation	1.5 mL solution per PFS
Dose	300 mg once weekly
Route of Administration	SC

7.2 Packaging and Labeling

The Sponsor will provide the Investigator with packaged volanesorsen labeled (ISIS 304801) in accordance with specific country regulatory requirements.

7.3 Study Drug Accountability

The study staff is required to document the receipt, dispensing, and return/destruction of volanesorsen provided by the Sponsor. The Study Center must return all unused volanesorsen to the Sponsor or designee. All used syringes must be disposed of as per the site's hazardous waste destruction policy.

8. TREATMENT OF PATIENTS

8.1 Volanesorsen Administration

For each individual patient, volanesorsen will be administered subcutaneously as a single 1.5 mL injection once weekly for Weeks 1-52.

Patients should receive 1 dose per week, with weeks always defined relative to Study Day 1. For example if a patient receives the first dose on a Monday, subsequent doses should be given on Mondays, if possible. If a patient misses an injection, or if dosing on the usual day is not

possible, the patient can reschedule the injection provided that 2 doses are administered at least 2 days apart.

Every effort should be made to ensure the previous week's dose is given 7 days prior to a scheduled clinic visit.

Please refer to the Study Drug Manual provided by the Sponsor for more detailed instructions for volanesorsen preparation and administration.

8.2 Other Protocol-Required Drugs

There are no other protocol-required drugs (Section 6.2.5).

8.3 Other Protocol-Required Treatment Procedures

There are no other protocol required treatment procedures for this study.

8.4 Treatment Precautions

There are no specific treatment precautions required for this study.

8.5 Safety Monitoring Rules

Please refer also to the 'Guidance for Investigator' section of the Investigator's Brochure.

For the purposes of safety monitoring baseline is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 (e.g., qualification assessments or assessments from final visit of the index study if used for qualification).

In addition to the standard monitoring of clinical safety parameters, the following guidelines are provided for the monitoring of selected parameters chosen based on preclinical and clinical observations.

Confirmation Guidance: At any time during the study (Treatment or Post-Treatment Periods), the initial clinical laboratory results meeting the safety monitoring or stopping criteria presented below **must be confirmed** by performing measurements (ideally in the same laboratory that performed the initial measurement) on new specimens. All new specimen collections should take place as soon as possible (ideally within 3 days of the initial collection). For stopping rules, if the initial laboratory result is observed during the Treatment Period, the results from the retest **must be available** prior to administering the next dose of volanesorsen.

In addition to the safety monitoring parameters listed below, the Sponsor may request confirmation of additional lab values.

Re-dosing Guidance: Patients with initial laboratory test values that reach a stopping rule must not be re-dosed until the re-test results are available. In general, patients who do not meet the stopping rules based upon retest may continue dosing. However, the Investigator and the Sponsor Medical Monitor (or appropriately qualified designee) should confer as to whether additional close monitoring of the patient is appropriate. If any of the stopping criteria described below (refer to Sections 8.6.1 to 8.6.3) are met, the patient will be permanently discontinued from further treatment with volanesorsen, evaluated fully as outlined below and in consultation with the Sponsor Medical Monitor or appropriately qualified designee, and will be followed up in accordance with Section 8.8 of the protocol.

8.5.1 Safety Monitoring Rules for Liver Chemistry Tests

The following rules are adapted from the draft guidance for industry, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," issued by the U.S. Department of Health and Human Services, Food and Drug Administration, July 2009. For a definition of Baseline please refer to guidance in Section 8.5 above.

In the event of an ALT or AST measurement that is > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) at any time during the study (Treatment or Post-Treatment Period), the initial measurement(s) should be confirmed as described above. Additional confirmatory measurements should also be performed if ALT or AST levels increase to 5 x ULN.

Frequency of Repeat Measurements: Patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) should have their liver chemistry tests (ALT, AST, alkaline phosphatase (ALP), international normalized ratio (INR) and total bilirubin) retested at least once-weekly until ALT and AST levels become ≤ 1.2 x ULN or 1.2 x baseline value if the baseline value was > ULN.

Further Investigation into Liver Chemistry Elevations: For patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), the following evaluations should be performed:

1. Obtain a more detailed history of symptoms and prior and concurrent diseases
2. Obtain further history for concomitant drug use (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
3. Obtain a history for exposure to environmental chemical agents and travel
4. Serology for viral hepatitis (HAV IgM, HBsAg, HCV antibody, CMV IgM, and EBV antibody panel)
5. Serology for autoimmune hepatitis (e.g., antinuclear antibody [ANA])

Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic CT or MRI scans, may be performed at the discretion of the Investigator, in consultation with the Sponsor Medical Monitor. Repetition of the above evaluations should be considered if a patient's ALT and/or AST levels reach 5 x ULN.

8.5.2 Safety Monitoring Rules for Platelet Count Results

If a patient's platelet count falls by 30% or greater from baseline and the absolute platelet count is 75,000/mm^3 or less, then the patient's platelet counts should be monitored more frequently. The frequency of monitoring and additional lab tests will be determined by the Investigator in consultation with the Sponsor Medical Monitor or designee.

8.5.3 Safety Monitoring for Minor Bleeding Events

Minor bleeding events are those that do not fulfill the criteria for major bleeding or clinically relevant, non-major bleeding events (which are defined in Section 8.6.3), for example excess

bruising, petechiae, gingival bleeding on brushing teeth. If a minor bleeding event occurs, the Investigator must notify the Sponsor Medical Monitor and additional testing of coagulation parameters activated partial thromboplastin time (aPTT), prothrombin time (PT), INR and platelet count should be performed.

8.5.4 Safety Monitoring for Constitutional Symptoms

Patients will be instructed to promptly report any signs of symptoms of fever or constitutional symptoms that may arise during the study and the Investigator should closely evaluate all potential causes, including concomitant illness. Patients that experience persistent constitutional symptoms should be discussed with the Sponsor Medical Monitor or designee to determine whether additional monitoring or laboratory tests are required.

8.5.5 Safety Monitoring for LDL-C Elevations

Beginning at Week 13, laboratory alerts will be in place to notify the Investigator if a patient has a low-density lipoprotein-cholesterol (LDL-C) > 160 mg/dL (> 130 mg/dL for patients with T2DM) on two consecutive visits. If this occurs, LDL-C values for this patient will be unblinded for the remainder of the study and the Investigator will be encouraged to initiate/adjust treatment to lower LDL-C according to country-specific guidelines (e.g., initiate statin therapy or increase the statin dose for patients who are already on treatment).

8.5.6 Acute Pancreatitis

If a patient has an episode of acute pancreatitis, dosing with study drug should be suspended temporarily until the patient is clinically stable. The suitability of the patient for continued dosing and the need for any modification to treatment schedule (refer to Section 8.7) will be determined by the Investigator in consultation with the Study Medical Monitor.

8.6 Stopping Rules

For the purposes of stopping rules baseline is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1.

8.6.1 Stopping Rules for Liver Chemistry Elevations

In the event of laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor,** dosing of a patient with volanesorsen will be stopped permanently; values that are not confirmed due to failure to retest or missing lab values will be presumed confirmed:

1. ALT or AST > 8 x ULN, which is confirmed
2. ALT or AST > 5 x ULN, which is confirmed and persists for ≥ 2 weeks
3. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed **and** total bilirubin > 2 x ULN or INR > 1.5
4. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed, and the new appearance (i.e., onset coincides with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> ULN) felt by the Investigator to be potentially related to hepatic inflammation

8.6.2 Stopping Rules for Renal Function Test Results

In the event of a persistent elevation that is observed over 2 consecutive weeks, for any of the three criteria below, dosing of a patient with volanesorsen may be stopped temporarily:

1. Serum creatinine increase that fulfill all of the following criteria: ≥ 0.3 mg/dL (26.5 µmol/L) and ≥ 40% above baseline creatinine values and > ULN
2. Proteinuria, dipstick 2 + (confirmed by dipstick retest and then further confirmed by a quantitative total urine protein measurement of > 1.0 g/24 hour)
3. Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault ≤ 40 mL/min that is confirmed by a 24 hour urine collection

The possible dosing re-initiation or follow-up schedule for any events meeting either of these criteria will be determined by the Investigator **in consultation with** the Sponsor Medical Monitor or designee.

8.6.3 Stopping Rule for Platelet Count Results

In the event of a platelet count less than 50,000/mm^{3}that is associated with major bleeding or clinically relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with volanesorsen will be stopped permanently. The follow-up schedule for any events meeting this stopping criterion will be determined by the Investigator in consultation with the Sponsor Medical Monitor.

In the event of a platelet count less than 50,000/mm^3, and in the absence of major bleeding or clinically relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with volanesorsen should be suspended temporarily until the platelet count has recovered to ≥ 100,000/mm^3. The suitability of the patient for continued dosing and the need for any modification to treatment schedule (refer to Section 8.7) will be determined by the Investigator in consultation with the Study Medical Monitor and will be based on factors such as the original rate of decline in the patient's platelet count, whether any bleeding events were experienced by the patient, and the speed of recovery of platelet count upon holding of dosing.

If after the first dosing re-challenge the platelet count again falls below 50,000/mm^3, then dosing of the patient must be held until the platelet count again returns to at least 100,000/mm^3. The suitability of the patient for continued dosing and the need for any further modification to treatment schedule or dose (refer to Section 8.7) will be re-examined by the Investigator in consultation with the Study Medical Monitor based on (at least) the factors mentioned above.

If after the second re-challenge the platelet count falls below 50,000/mm^3 and is subsequently confirmed (see Section 8.5), dosing with volanesorsen will be stopped permanently. The follow-up schedule for any events meeting this stopping criterion will be determined by the Investigator in consultation with the Study Medical Monitor.

Definition of Major Bleeding Events (Schulman et al. 2005):

- Fatal bleeding, and/or
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarterial or pericardial, or intramuscular with compartment syndrome, and/or
- Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more within 24 hours, or leading to transfusion of two or more units of whole or red cells

Definition of Clinically Relevant, Non-Major Bleeding Events (Schulman et al. 2005):

1. Multiple-source bleeding
2. Spontaneous hematoma > 25 cm^2
3. Excessive wound hematoma (not injection site related)
4. Macroscopic hematuria (spontaneous or lasting > 24 hours if associated with an intervention)
5. Spontaneous rectal bleeding; epitasis, gingival bleeding, hemoptysis, hematemesis
6. Bleeding after venipuncture for > 5 minutes

8.7 Adjustment of Dose Frequency

Dose adjustments, including dose interruptions, and/or decreasing the dose frequency will be allowed for safety and tolerability. Any proposed adjustment to treatment schedule must be discussed with, and approved by, the Study Medical Monitor prior to initiation. Up to two adjustments in the treatment schedule may be allowed for patients that are unable to tolerate the once weekly dose (for example if platelet counts fall below 50,000/mm^3 as described in Section 8.6.3). If the patient remains stable after adjustment, they may be cautiously returned to the original once weekly regimen after consultation with the Study Medical Monitor.

Patients may be dose paused in response to AEs after consultation with Study Medical Monitor.

8.8 Discontinuation of Study Treatment

A patient must permanently discontinue study treatment for any of the following:

- The patient becomes pregnant. Report the pregnancy according to instructions in Section 9.5.4
- The patient withdraws consent
- The patient experiences an AE that necessitates permanent discontinuation of study treatment
- The patient develops laboratory test abnormalities that meet any of the stopping rules listed in Section 8.6

The reason for discontinuation of study treatment must be recorded in the CRF and source documentation.

8.8.1 Follow-up Visits for Early Termination from Treatment Period

Any patient who discontinues early from the Treatment Period should be strongly encouraged to attend applicable landmark visits at Weeks 12, 13, 25, 26, and 51, 52 (calculated based on the time elapsed since Day 1) to collect fasting lipid panels and conduct safety assessments in accordance with the schedule of procedures in Appendix A. Any patient who discontinues treatment after Week 44 should also be strongly encouraged to attend a final follow-up visit (Week 65 visit assessments) approximately 13 weeks after their last dose of Study Drug, in addition to the applicable landmark visits.

If the patient declines or is unable to participate in the above, an early termination (ET) visit (Week 52 visit assessments) should be performed at the time of withdrawal, at a minimum, and ideally within 2 weeks from the last dose of Study Drug.

8.8.2 Follow-up Visits for Early Termination from Post-Treatment Follow-up Period

The patient who requests to withdraw from the study during the Post-Treatment Follow-up Period should be encouraged to undergo a final follow-up visit (Week 65, see Appendix A) prior to leaving the study.

If a patient withdraws due to an AE at any time during the study, the Investigator should arrange for the patient to have appropriate follow-up until the AE has resolved or stabilized.

8.9 Withdrawal of Patients from the Study

Patients must be withdrawn from the study for any of the following:

- Withdrawal of consent
- The patient is unwilling or unable to comply with the protocol

Other reasons for withdrawal of patients from the study might include:

- At the discretion of the Investigator for medical reasons
- At the discretion of the Investigator or Sponsor for noncompliance
- Significant protocol deviation

All efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information, including the reason for withdrawal from Study, must be recorded in the CRF.

Any patient who withdraws consent to participate in the study will be removed from further treatment and study observation immediately upon the date of request. These patients should be encouraged to complete the ET study procedures and observations at the time of withdrawal (see Section 8.8 and Appendix A).

For patients withdrawn for reasons other than withdrawal of consent every effort should be made to complete the early termination study procedures and observations at the time of withdrawal (see Section 8.8 and Appendix A).

8.10 Concomitant Therapy and Procedures

The use of concomitant therapies or procedures defined below must be recorded on the patient's CRF. AEs related to administration of these therapies or procedures must also be documented on the appropriate CRF.

8.10.1 Concomitant Therapy

A concomitant therapy is any non-protocol specified drug or substance (including over-the-counter medications, herbal medications and vitamin supplements) administered between signing informed consent and completion of the post-treatment follow-up period. All concomitant medications/treatments and significant non-drug therapies (including supplements and assistive devices) received by a patient, including changes in the patient's current medications, must be recorded in the patient's source documents and CRF. Patients taking over the counter (OTC) omega-3 fatty acids should make every effort to remain on the same brand throughout the study.

Allowed Concomitant Therapy

Any medications deemed necessary by the Investigator are allowed except those listed in the disallowed concomitant therapy.

Disallowed Concomitant Therapy

No lipid lowering therapies (e.g., fibrates, niacin, fish oil or other products containing omega-3 fatty acids [including OTC preparations]), glucacon-like peptide-1 (GLP-1) agonists, Glybera, or systemic corticosteroids may be started or adjusted after baseline qualification. Doses of existing oral anti-diabetic medication, oral contraceptives, hormone replacement therapy, anticoagulants, or drugs or dietary supplements with potential lipid-altering effects should not be adjusted. Study patients are prohibited from receiving other experimental agents during the study. This includes marketed agents at experimental dosages that are being tested for the treatment of hypertriglyceridemia.

Patients should consult with the Site Investigator or designee prior to initiating any new medication, including non-prescription or herbal compounds or any other non-drug therapy.

8.10.2 Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between signing of informed consent and Week 65 visit.

Disallowed Concomitant Procedure

Plasma apheresis is not allowed during the study.

8.11 Treatment Compliance

Compliance with treatment dosing is to be monitored and recorded by Study Center staff. The Study Center staff is required to document the receipt, dispensing, and return/destruction of volanesorsen. Patients that are self-administering volanesorsen at home must record treatment in a dosing diary that will be reviewed periodically by Study Center staff and the Clinical Monitor.

9. SERIOUS AND NON-SERIOUS ADVERSE EVENT REPORTING

9.1 Sponsor Review of Safety Information

Safety information will be collected, reviewed, and evaluated by the Sponsor in accordance with the Safety Management Plan throughout the conduct of the clinical trial.

9.2 Regulatory Requirements

The Sponsor is responsible for regulatory submissions and reporting to the Investigators of serious adverse events (SAEs) including suspected unexpected serious adverse reactions (SUSARs) per the International Conference on Harmonization (ICH) guidelines E2A and ICH E6. Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines.

Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) will be notified of any SAE according to applicable regulations. The Data and Safety Monitoring Board (DSMB) will be notified of any SAE as specified in the DSMB charter.

The Sponsor or designee will evaluate the available information and decide if there is a reasonable possibility that volanesorsen caused the AE and, therefore, meets the definition of a SUSAR.

The following table identifies the SAEs that the Sponsor or designee will not report on an individual basis in an expedited manner because they are anticipated to occur in the study population independent of volanesorsen exposure. The Investigator still has the responsibility to report all SAEs to the Sponsor as described in Sections 9.4.1 to 9.4.3.5.

Table 2 Expected Event for the Protocol Defined Population by Preferred Term and the Expected Incidence

Preferred Term	Expected Incidence in the Protocol Defined Population (Gaudet et al. 2010 and 2013)
Pancreatitis associated events including the PTs of hereditary pancreatitis, pancreatitis, pancreatitis acute, pancreatitis chronic, pancreatitis necrotizing, pancreatitis relapsing	0.2-0.35 events per patient-year

Fatal pancreatitis associated events will be considered as unexpected and are reportable. The Sponsor and DSMB will monitor non-fatal pancreatitis associated SAEs using the incidence rate of the event compared to the rate expected in a non-volanesorsen exposed population. If the aggregate analysis indicates that an event is occurring significantly more frequently or at a greater severity than expected, then the event will be reported.

SAEs not specified in the table will be evaluated on case by case basis to determine whether there is a reasonable possibility that the drug caused the event. If the event is considered by the Sponsor or designee to meet the definition of a SUSAR the event will be reported.

9.3 Definitions

9.3.1 Adverse Event

An adverse event is any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the study or use of investigational drug product, whether or not the AE is considered related to the investigational drug product.

9.3.2 Adverse Reaction and Suspected Adverse Reaction

An adverse reaction is any adverse event caused by volanesorsen.

A suspected adverse reaction is any adverse event for which there is a reasonable possibility that volanesorsen drug caused the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

9.3.3 Serious Adverse Event (SAE)

A serious adverse event is any adverse event that in the view of either the Investigator or Sponsor, meets any of the following criteria:

- Results in death
- Is life threatening: that is, poses an immediate risk of death at the time of the event

An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Hospitalization is defined as an admission of greater than 24 hours to a medical facility and does not always qualify as an AE
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly or birth defect in the offspring of the patient (whether the patient is male or female)
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

9.4 Monitoring and Recording Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the study (i.e., before informed consent) should be recorded as Medical History and not recorded as AEs unless the pre-existing condition worsened. The Investigator should always group signs and symptoms into a single term that constitutes a **single unifying diagnosis** if possible.

9.4.1 Serious Adverse Events

In the interest of patient safety, and in order to fulfill regulatory requirements**,** all SAEs (regardless of their relationship to volanesorsen) should be reported to the Sponsor or designee within 24 hours of the Study Center's first knowledge of the event. The collection of SAEs will begin after the patient signs the informed consent form and stop at the end of the patient's follow-up period which is defined as the Week 65 visit. When the Investigator is reporting by telephone, it is important to speak to someone in person versus leaving a message. An Initial Serious Adverse Event Form should be completed and a copy should be faxed to the Sponsor or designee.

Detailed information should be actively sought and included on Follow-Up Serious Adverse Event Forms as soon as additional information becomes available. All SAEs will be followed until resolution. SAEs that remain ongoing past the patient's last protocol-specified follow-up visit will be evaluated by the Investigator and Sponsor. If the Investigator and Sponsor agree the patient's condition is unlikely to resolve, the Investigator and Sponsor will determine the follow-up requirement.

9.4.2 Non-Serious Adverse Events

The recording of non-serious AEs will begin after the patient signs the informed consent form and will stop at the end of the patient's follow-up period, which is defined as the Week 65 visit. The Investigator will monitor each patient closely and record all observed or volunteered AEs on the Adverse Event Case Report Form.

9.4.3 Evaluation of Adverse Events (Serious and Non-Serious)

The Investigator's opinion of the following should be documented on the Adverse Event Case Report Form:

9.4.3.1 Relationship to the Study Drug

The event's relationship to volanesorsen is characterized by one of the following:

- **Related:** There is clear evidence that the event is related to the use of volanesorsen e.g., confirmation by positive re-challenge test
- **Possible:** The event cannot be explained by the patient's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and volanesorsen administration
- **Unlikely/Remote:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to volanesorsen administration and/or exposure suggests that a causal relationship is unlikely (For reporting purposes, Unlikely/Remote will be grouped together with Not Related)

- **Not Related:** The event can be readily explained by the patient's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and volanesorsen

9.4.3.2 Severity

The severity of AEs and SAEs will be graded based on criteria from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010 (refer to Appendix D). Any AE not listed in Appendix D will be graded as follows:

- **Mild:** The event is easily tolerated by the patient and does not affect the patient's usual daily activities
- **Moderate:** The event causes the patient more discomfort and interrupts the patient's usual daily activities
- **Severe:** The event is incapacitating and causes considerable interference with the patient's usual daily activities

If the event is an SAE, then all applicable seriousness criteria must be indicated (criteria listed in Section 9.3.3).

9.4.3.3 Action Taken with Volanesorsen

Action taken with volanesorsen due to the event is characterized by one of the following:

- **None:** No changes were made to volanesorsen administration and dose
- **Permanently Discontinued:** Volanesorsen was discontinued and not restarted
- **Temporarily Interrupted, restarted – same dose:** Dosing was temporarily interrupted or delayed due to the AE and restarted at the same dose
- **Reduced schedule:** Dosing frequency was reduced

9.4.3.4 Treatment Given for Adverse Event

Any treatment (e.g., medications or procedures) given for the AE should be recorded on the Adverse Event Case Report Form (treatment should also be recorded on the concomitant treatment or ancillary procedures CRF as appropriate).

9.4.3.5 Outcome of the Adverse Event

If the event is a non-serious AE then the event's outcome is characterized by one of the following:

- **AE Persists:** Patient terminates from the trial and the AE continues
- **Recovered:** Patient recovered completely from the AE
- **Became Serious:** The event became serious (the date that the event became serious should be recorded as the Resolution Date of that AE and the Onset Date of the corresponding SAE)
- **Change in Severity** (if applicable): AE severity changed

If the event is a SAE then the event's outcome is characterized by one of the following:

- **Ongoing:** SAE continuing
- **Persists (as non-serious AE):** Patient has not fully recovered but the event no longer meets serious criteria and should be captured as an AE on the non-serious AE eCRF (the SAE resolution date should be entered as the date of onset of that AE)
- **Recovered:** Patient recovered completely from the SAE (the date of recovery should be entered as the SAE resolution date)
- **Fatal:** Patient died (the date of death should be entered as the SAE resolution date)

9.4.4 Adjudication Committees

All SAEs that occur during the study that are consistent with a major acute cardiovascular event (MACE) will be adjudicated by a blinded, independent committee as outlined in the MACE Adjudication Charter.

All AEs and SAEs that occur during the study that are consistent with an event of acute pancreatitis will be adjudicated by a blinded, independent committee according to the Atlanta classification of acute pancreatitis (Banks et al. 2013) and as outlined in the Pancreatitis Adjudication Charter. In addition, data for prior episodes of acute pancreatitis or suspected pancreatitis will be collected by review of each patient's medical chart and these events will also be adjudicated.

9.5 Procedures for Handling Special Situations

9.5.1 Abnormalities of Laboratory Tests

Clinically significant abnormal laboratory test results may, in the opinion of the Investigator, constitute or be associated with an AE. Examples of these include abnormal laboratory results that are associated with symptoms, or require treatment, e.g., bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac arrhythmias due to hyperkalemia. Whenever possible, the underlying diagnosis should be listed in preference to abnormal laboratory values as AEs. Clinically significant abnormalities will be monitored by the Investigator until the parameter returns to its baseline value or until agreement is reached between the Investigator and Sponsor Medical Monitor. Laboratory abnormalities deemed not clinically significant (NCS) by the Investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator should not be deemed NCS on the laboratory sheet.

The Investigator is responsible for reviewing and signing all laboratory reports. The signed clinical laboratory reports will serve as source documents and should include the Investigator's assessment of clinical significance of out of range/abnormal laboratory values.

9.5.2 Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the patient is hospitalized; the Study Center must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the patient's consent to participate in the study
- The condition that required the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the patient's consent to participate in the study and the timing of the procedure or treatment
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission

9.5.3 Dosing Errors

Volanesorsen dosing errors should be documented as Protocol Deviations. A brief description should be provided in the deviation, including whether the patient was symptomatic (list symptoms) or asymptomatic, and the event accidental or intentional.

Dosing details should be captured on the Dosing Case Report Form. If the patient takes a dose of volanesorsen that exceeds protocol specifications and the patient is symptomatic, then the symptom(s) should be documented as an AE and be reported per Section 9.4.

Should an overdose occur, the Investigator or designee should refer to the Guidance to Investigator's section of the Investigator's Brochure and contact the Sponsor or designee within 24 hours.

9.5.4 Contraception and Pregnancy

Male patients and female patients of childbearing potential must continue to use appropriate contraception with their partners, or refrain from sexual activity, as described in Section 6.3.1.

If a patient becomes pregnant or a pregnancy is suspected, or if a male patient makes or believes that he has made someone pregnant during the study, then the Study Center staff must be informed immediately. An Initial Pregnancy Form should be submitted to the Sponsor or designee **within 24 hours** of first learning of the occurrence of pregnancy. Follow-up information including delivery or termination is reported on Follow-up Pregnancy Forms and reported within 24 hours.

Payment for all aspects of obstetrical care, child or related care will be the patient's responsibility.

Female patients: If a suspected pregnancy occurs while on the study (including follow-up), a pregnancy test will be performed. The patient with a confirmed pregnancy will be immediately withdrawn from treatment with volanesorsen. However, the patient will be encouraged to complete the post-treatment follow-up portion of the study to the extent that study procedures do not interfere with the pregnancy. Regardless of continued study participation, the study physician will assist the patient in getting obstetrical care and the progress of the pregnancy will be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the Study Center and

Sponsor may require access to the mother and infant's medical records for an additional 8 weeks after birth.

Male patients: The progress of the pregnancy in a male patient's partner should be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, **the Study Center and Sponsor may request access to the mother and infant's medical records for an additional 8 weeks after birth**. Follow-up will be performed to the extent permitted by applicable regulations and privacy considerations.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints

For fasting lipid measurements, the values at Month 3 analysis time point are defined as the average of Week 12 (Day 78) and Week 13 (Day 85) fasting assessments, the values of Month 6 analysis time point is at the end of Month 6 are defined as the average of Week 25 (Day 169) and Week 26 (Day 176) fasting assessments, and the values at the Month 12 analysis time point are defined as the average of Week 51 (Day 351) and Week 52 (Day 358) fasting assessments.

10.1.1 Efficacy Endpoints

- Percent change and absolute change from baseline in fasting TG
- Frequency and severity of patient reported abdominal pain during the treatment period
- Percent change and change from baseline in other fasting lipid measurements including total cholesterol, non-HDL-C, apoB, HDL-C, apolipoprotein A-1 [apoA-1], VLDL-C, and LDL-C
- Percent change from baseline in fasting total apolipoprotein C-III
- Quality of Life questionnaires (EQ-5D, SF-36)
- Adjudicated acute pancreatitis event rate

10.1.2 Safety Endpoints

- Adverse events including adjudicated events of pancreatitis and MACE
- Vital signs and weight
- Physical examinations
- Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis)
- Echocardiography
- Electrocardiograms (ECGs)
- Use of concomitant medications
- MRIs

10.2 Sample Size

No sample size calculations were performed as this is an extension study to the double-blind, placebo-controlled ISIS 304801-CS6 study. Approximately 50 patients may be eligible to enroll into this study.

10.3 Populations

Full Analysis Set (FAS): All patients who are enrolled and have a baseline TG assessment. The FAS represents the practically-feasible intent-to-treat (ITT) population as delineated in ICH Guideline E9.

Per Protocol Set (PPS): Subset of the FAS who received 9 of first 13 scheduled doses of volanesorsen and with no significant protocol deviations that would be expected to affect efficacy and PD assessments. The detailed criteria will be specified and finalized prior to the final database lock.

Safety Set: All patients who are enrolled and receive at least one dose of volanesorsen.

PK Population: All patients who are enrolled, receive at least one dose of volanesorsen, and have at least one evaluable PK sample collected, analyzed, and reported.

10.3 Definition of Baseline

Definitions of baseline are given below for the purposes of the final analysis.

For fasting lipid measurements, two baselines are defined for each patient: index study baseline and the baseline in this open label study, which is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 (e.g., qualification assessments or assessments from final visit of the index study if used for qualification).

For other measurements, baseline for patients on active treatment in the index study will be the index study baseline. For patients on placebo in the index study, baseline for safety will be the last non-missing assessment prior to the first dose of Study Drug.

10.4 Interim Analysis

An interim analysis may be conducted after the database of index study is locked and unblinded. Both safety and efficacy information from this study may be summarized during this interim analysis. Efficacy analyses will be detailed in the SAP.

10.5 Planned Methods of Analysis

All eCRF data, lab data transfers, as well as any outcomes derived from the data, will be provided in the patient data listings. Patient data listings will be presented for all patients enrolled into the study. Descriptive summary statistics including n, mean, median, standard deviation, standard error, interquartile range (25th percentile, 75th percentile), and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data by treatment group. Where appropriate, p-values will be reported. All statistical tests will be conducted using 2-sided tests with 5% Type I error rates unless otherwise stated.

All efficacy endpoints will be assessed in the FAS and PPS. All safety assessments will be performed on the Safety Set. PK endpoints will be assessed in the PK Set as applicable.

10.5.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics by treatment group. The patient disposition will be summarized by treatment group of the index study. All patients enrolled will be included in a summary of patient disposition.

10.5.2 Safety Analysis

Treatment duration and amount of Study Drug received will be summarized by treatment group of the index study.

Patient incidence rates of AEs will be tabulated by MedDRA system organ class, MedDRA preferred term, and treatment group of the index study. Narratives of treatment emergent deaths, serious and significant AEs, including early withdrawals due to AEs, will also be provided.

All treatment emergent AEs, all treatment emergent AEs potentially related to Study Drug, all treatment emergent serious AEs, and all treatment emergent serious AEs potentially related to Study Drug will be summarized.

Injection Site Reactions (ISRs) will be summarized by treatment group of the index study, MedDRA preferred term and severity.

Independently adjudicated events of MACE and pancreatitis will be summarized by treatment group of the index study.

Laboratory tests to ensure patient safety including chemistry panel, complete blood count (CBC) with differential, coagulation panel, IM, complement etc., will be summarized by study visits by treatment group of the index study. These safety variables will also be presented as change and percent change from baseline over time after study drug administration, as appropriate.

Vital signs, weight, ECG measures, echocardiography assessments, and MRI assessments will be tabulated by treatment group of the index study.

10.5.3 Efficacy Analysis

Percent change and change from baseline to Month 3, Month 6, and Month 12 in fasting TG will be summarized by treatment group of the index study. Response rate of patients with fasting plasma TG < 750 mg/dL or achieving fasting TG $\geq 40\%$ reduction from baseline at Month 3, Month 6, and Month 12 will be summarized. Response analysis will also be conducted using a range of fasting plasma TG thresholds for determination of responder status.

Percent change and change from baseline to Month 3, Month 6, and Month 12 will also be summarized by treatment group of the index study for other fasting lipid measures including non-HDL-C, apoB, HDL-C, apoA-1, VLDL-C, and LDL-C, total cholesterol, and fasting total apoC-III.

The incremental effects of volanesorsen on lipid measures will be explored and the association between changes in lipid parameters and total amount of drug received will be examined, as appropriate.

Frequency and severity of patient reported abdominal pain, adjudicated acute pancreatitis event rate, and quality of life assessments will be summarized by treatment group of the index study.

Additional details of the analyses to be conducted will be provided in the SAP.

10.5.4 Pharmacokinetic and Immunogenicity Analysis

10.5.4.1 Pharmacokinetic Analysis

For all patients, pre-dose and post-treatment volanesorsen plasma concentrations will be summarized using descriptive statistics, with stratification by their prior treatment in Study ISIS 304801-CS6 and IM status.

For patients in the PK subgroup only, non-compartmental PK analysis of volanesorsen will be carried out on each individual patient data set using data collected in the open label extension (OLE) study from the intensive PK subgroup, following a single dose (i.e., single-dose PK) or multiple doses (i.e., steady-state PK), depending on their earlier treatment in the index study. On Week 1 Day 1 of the OLE study, patients who received placebo in the index study will receive the first treatment of volanesorsen (single-dose PK), while patients who received volanesorsen in the index study had been on volanesorsen treatment for twelve months, thus the PK data collected from these patients reflect steady-state PK. The maximum observed drug concentration (C_{max}) and the time taken to reach C_{max} (T_{max}) will be obtained directly from the concentration-time data. Area under the plasma concentration-time curve from time zero to 24 hours ($AUC_{0\text{-}24hr}$) will be calculated using the linear trapezoidal rule. Apparent systemic (plasma) clearance after SC administration ($CL/F_{0\text{-}24hr}$) will be calculated from $CL/F_{0\text{-}24hr}$ = Actual Dose/$AUC_{0\text{-}24hr}$. Mean residence time (MRT) from time zero to 24 hours after the SC administration will be calculated from the equation, $MRT_{0\text{-}24hr} = AUMC_{0\text{-}24hr}/AUC_{0\text{-}24hr}$, where $AUMC_{0\text{-}24hr}$ is the area under the moment plasma concentration-time curve from time zero to 24 hours after the SC administration. Other PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist.

Plasma PK parameters will be summarized using descriptive statistics, with and without stratification by their prior treatment in Study ISIS 304801-CS6 and IM status. Additional details regarding the PK analysis will be described in the SAP.

Population PK, PK/PD, and covariate analysis may be performed if deemed appropriate, and results will be reported separately.

10.5.4.2 Immunogenicity Analysis

Immunogenicity (IM) results (screen positive/negative, confirmed positive/negative or not evaluable, and when applicable, titer of anti-volanesorsen antibodies) before, during, and after treatment with study drug (volanesorsen) (i.e., sample [anti-drug antibody] ADA status) will be listed by their prior treatment in Study ISIS 304801-CS6 and study day. Subject ADA status (positive/negative or not evaluable) for all evaluable patients, along with the study day associated

with the first positive IM status emerged (T_{first}, i.e., onset of ADA development), the last positive IM status observed (T_{last}), the duration of ADA response (number of days between T_{first} and T_{last}) if appropriate, the last ADA sample collection day, and subject maximum titer if applicable, will be listed by their prior treatment in Study ISIS 304801-CS6 and study day. Subjects with positive anti-volanesorsen antibody status may be further classified (when applicable) as being either 'persistent', 'transient', or 'not determinable', if deemed appropriate.

Additionally, the sample and subject IM incidence (number) and incidence rate (percent) will be summarized as the total number and percent of evaluated subjects with antibody negative, positive, and unknown status by their prior treatment in Study ISIS 304801-CS6. Furthermore, onset, duration, and titer of the ADA response, if applicable, will be summarized as median, quartiles (25% and 75%), and range.

Additional details regarding the IM data analysis will be described in the SAP.

Potential relationships between immunogenicity results (e.g., IM status) and selected efficacy (e.g., % change in fasting TG from baseline at 3-, 6-, and 12-month endpoints), safety, and PK (e.g., C_{trough}) measures will be evaluated using graphical analysis and statistical analysis. These analyses will be either conducted and included in the study report, or data pooled and analyzed from all available Phase II and III studies and reported separately

11. INVESTIGATOR'S REGULATORY OBLIGATIONS

11.1 Informed Consent

The written informed consent document should be prepared in the language(s) of the potential patient population, based on an English version provided by the Sponsor.

Before a patient's participation in the trial, the Investigator is responsible for obtaining written informed consent from the patient after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific qualification procedures or any Study Drug are administered. The patient must be given sufficient time to consider whether to participate in the study.

The acquisition of informed consent and the patient's agreement or refusal to notify his/her primary care physician should be documented in the patient's medical records and the informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion (not necessarily an Investigator). The original signed informed consent form should be retained in the Study Master File and in any other locations required by institutional policy, and a copy of the signed consent form should be provided to the patient.

11.2 Ethical Conduct of the Study

The Guidelines of the World Medical Association (WMA) Declaration of Helsinki dated October 2002 the applicable regulations and guidelines of current Good Clinical Practice (GCP) as well as the demands of national drug and data protection laws and other applicable regulatory requirements will be strictly followed.

11.3 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent form, other written patient information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by the Sponsor before recruitment of patients into the study and shipment of volanesorsen. A copy of the written approval of any other items/materials that must be approved by the Study Center or IEC/IRB must also be received by the Sponsor before recruitment of patients into the study and shipment of Study Drug. The Investigator's Brochure must be submitted to the IEC/IRB for acknowledgement.

The Investigator must submit to and, where necessary, obtain approval from the IEC/IRB, for all subsequent protocol amendments and changes to the informed consent document. The Investigator should notify the IEC/IRB of deviations from the protocol in accordance with ICH GCP Section 4.5.2. The Investigator should also notify the IEC/IRB of serious adverse events occurring at the Study Center and other adverse event reports received from the Sponsor, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study. Copies of the Investigator's reports, all IEC/IRB submissions and the IEC/IRB continuance of approval must be sent to the Sponsor.

11.4 Patient Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained. On the case report forms (CRF) or other documents submitted to the Sponsor, patients should be identified by unique initials and a patient study number only. Documents that are not for submission to the Sponsor (e.g., signed informed consent forms) should be kept in strict confidence by the Investigator.

In compliance with Federal and local regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the patient to permit named representatives to have access to his/her study-related records without violating the confidentiality of the patient.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments

Protocol amendments must be made only with the prior approval of the Sponsor. Agreement from the Investigator must be obtained for all protocol amendments and amendments to the informed consent document. The regulatory authority and IEC/IRB must be informed of all amendments and give approval for any amendments likely to affect the safety of the patients or the conduct of the trial. The Investigator **must** send a copy of the approval letter from the IEC/IRB to the Sponsor.

12.2 Study Termination

The Sponsor reserves the right to terminate the study according to the terms of the site contract. The Investigator reserves the right to terminate their participation in the study, according to the terms of the site contract. The Investigator/Sponsor should notify the IEC/IRB in writing of the trial's completion or early termination and send a copy of the notification to the Sponsor.

12.3 Study Documentation and Storage

An electronic case report form (eCRF) utilizing an Electronic Data Capture (EDC) application will be used for this study.

The Investigator should ensure that all appropriately qualified persons to whom he/she has delegated trial duties are recorded on a Sponsor-approved Delegation of Site Responsibilities Form.

Source documents are original documents, data, and records from which the patient's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, imaging, and correspondence. In this study, CRFs may not be used as source documents.

The Investigator and Study Center staffs are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation in accordance with Section 8 of the ICH Guidelines (E6), suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Elements should include:

- Patient files containing completed CRFs, informed consents, and supporting copies of source documentation
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation and all correspondence to and from the IEC/IRB and the Sponsor
- If volanesorsen supplies are maintained at the Study Center, proof of receipt, volanesorsen Accountability Record, Return of volanesorsen for Destruction, final study volanesorsen reconciliation, and all volanesorsen-related correspondence

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

No study document should be destroyed without prior written agreement between the Sponsor or and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor.

12.4 Study Monitoring

The Sponsor representative and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the trial (e.g., CRFs and other pertinent data) provided that patient confidentiality is respected.

The Sponsor monitor is responsible for inspecting the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to patient medical records and other study-related records needed to verify the entries on the CRFs.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's Clinical Quality Assurance Department. Inspection of Study Center facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the trial conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

To ensure the quality of clinical data a clinical data management review will be performed on patient data received by the Sponsor. During this review, patient data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or Study Center notifications will be sent to the Study Center for completion and return to Sponsor.

The Principal Investigator will sign and date the indicated places on the CRF. These signatures will indicate that the principal Investigator inspected or reviewed the data on the CRF, the data queries, and the Study Center notifications, and agrees with the content.

12.5 Language

Case report forms must be completed in English. Generic names for concomitant medications should be recorded in English if possible, unless it is a combination drug, then record the trade name in English.

All written information and other material to be used by patients and investigative staff must use vocabulary and language that are clearly understood.

12.6 Compensation for Injury

The Sponsor maintains appropriate insurance coverage for clinical trials and will follow applicable local compensation laws. Patients will be treated and/or compensated for any study-related illness/injury in accordance with the information provided in the Compensation for Injury section of the Informed Consent document.

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14. APPENDICES

Appendix A Schedule of Procedures

Appendix A Schedule of Procedures

Study Period		Qual[a]	Treatment Period														Post Treatment Follow-up	
Study Week		-2 to -1	Wk 1		Wk 4	Wk 8	Month 3		Wk 19	Month 6		Wk 32	Wk 38	Wk 44	Month 12		Wk 58	Wk 65
							Wk 12	Wk 13		Wk 25	Wk 26				Wk 51	Wk 52 or ET		
Study Day		-14 to -7	1	2	22	50	78	85	127	169	176	218	260	302	351	358	400	449
Visit Window+/- Days		0	0	0	2	2	2	2	3	2	2	3	3	3	2	2	7	7
Informed Consent		X																
Outpatient Visit		X	X	X	X	X	X[g]	X		X[g]	X		X		X[g]	X		X
Inclusion/Exclusion Criteria		X																
Vital Signs + body weight (+ height on Day 1 only)		X	X		X	X		X			X		X			X		X
Physical Examination			X					X			X		X			X		X
12- lead ECG (triplicate)								X			X		X			X		X
MRI (liver/spleen)																X		
Echocardiography											X					X		
Urinalysis[b]		X	X[e]		X	X		X[e]	X[e]		X[e]	X[e]	X[e]	X[e]		X[e]	X[e]	X[e]
Blood Draw (Fasting)[b]	Chemistry Panel	X	X		X	X		X	X[g]		X	X[g]	X	X[g]		X	X[g]	X
	CBC with Differential	X	X		X	X		X	X[g]		X	X[g]	X	X[g]		X	X[g]	X
	Serum Lipid Panel	X	X		X	X	X[g]	X		X[g]	X		X		X[g]	X		X
	Coagulation (aPTT, PT, INR)					X		X			X		X			X		
	hsCRP, HbA1c, FPG		X					X			X					X		X
	Sedimentation Rate		X					X			X					X		X
	Complement (C5a, Bb)		X					X			X					X		X
	Plasma PK - Volanesorsen		X[h]	X	X	X		X			X		X			X		X
	Anti-Volanesorsen Antibodies		X		X	X		X			X		X			X		X
	FSH (women only, if applicable)																	
	Serum Pregnancy Test[c]	X				X		X			X		X			X		X
	Archived Serum & Plasma Samples[f]		X			X		X			X					X		X

Appendix A Schedule of Procedures *Continued*

Study Period	Qual[a]	Treatment Period														Post Treatment Follow-up	
Study Week	-2 to -1	Wk 1		Wk 4	Wk 8	Month 3		Wk 19	Month 6		Wk 32	Wk 38	Wk 44	Month 12		Wk 58	Wk 65
						Wk 12	Wk 13		Wk 25	Wk 26				Wk 51	Wk 52 or ET		
Study Day	-14 to -7	1	2	22	50	78	85	127	169	176	218	260	302	351	358	400	449
Visit Window+/- Days	0	0	0	2	2	2	2	3	2	2	3	3	3	2	2	7	7
Weekly Study Drug: SC Injection		X		X	X	X	X	X	X	X	X	X	X	X	X		
Symptom Diary (weekly)	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Food/Drink Diary (quarterly)[i]		X					X			X					X		X
Quality of Life Assessment(s)		X					X			X					X		X
Diet/Alcohol Counseling[d]	X	X		X	X		X			X		X			X	X	X
Adverse Events	X	X		X	X		X			X		X			X		X
Concomitant Medication	X	X		X	X		X			X		X			X		X

a Qualification procedures performed and the patient continues the symptom diary. Assessments from the Week 52 visit of the index study may be used for qualification purposes

b Blood samples to be collected after an overnight fast of at least 10 hours. During treatment period urine and blood samples will be collected prior to study drug administration. Does not apply to 24 hour PK blood draw

c Females of childbearing potential only

d To reinforce compliance to the diet and alcohol restrictions

e Expanded urinalysis (see Appendix B)

f Serum and plasma samples will be collected and stored for follow-up exploration of laboratory findings and/or adverse events (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.) in this or subsequent clinical studies of volanesorsen

g To be collected by either a clinical service, or Study Center as arranged by the Study Center personnel

h Full or abbreviated PK profile (see Appendix C)

i In addition to diary, patients will be contacted at random times during the study to review their current eating and drinking habits

Appendix B List of Laboratory Analytes

Appendix B List of Laboratory Analytes

Based on emerging data from this or future studies, additional tests not listed below may be performed on stored samples to better characterize the profile of volanesorsen or other similar oligonucleotides.

Clinical Chemistry Panel

- Sodium
- Potassium
- Chloride
- Bicarbonate
- Total protein
- Albumin
- Calcium
- Magnesium
- Phosphorus
- Glucose
- BUN
- Creatinine
- Uric Acid
- Total bilirubin
- Direct (conjugated) bilirubin
- Indirect (unconjugated) bilirubin
- ALT
- AST
- Alkaline phosphatase

Coagulation

- aPTT (sec)
- PT (sec)
- INR

Lipid Panel

- Total Cholesterol
- LDL-C
- HDL-C
- Triglycerides
- Non-HDL-C
- VLDL-C
- apoA-1
- apoB
- apoC-III

Hematology

- Red blood cells
- Hemoglobin
- Hematocrit
- MCV, MCH, MCHC
- Platelets
- White blood cells
- WBC Differential (% and absolute)
  - Neutrophils
  - Eosinophils
  - Basophils
  - Lymphocytes
  - Monocytes

Pharmacokinetics[1] & Immunogenicity

- Volanesorsen levels in plasma
- Anti-volanesorsen antibodies in plasma

Other assessments

- hsCRP
- Sedimentation Rate
- C5a, Bb
- De-lipidated free glycerol
- HbA1c, FPG

Urinalysis

- Color
- Appearance
- Specific gravity
- pH
- Protein
- Blood
- Ketones
- Urobilinogen
- Glucose
- Bilirubin
- Leukocyte esterase
- Nitrate
- Microscopic examination[2]

Additional Measures for Expanded Urinalysis

- Total protein (quantitative)
- Microalbumin
- β2-microglobulin

1 Plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, IM testing (or possibly for purposes of IM assay development and/or validation), or to assess other actions of volanesorsen with plasma constituents

2 Will be performed on abnormal findings unless otherwise specified

Appendix C Pharmacokinetic Sampling Schedule

Appendix C Pharmacokinetic Sampling Schedule

Blood samples for the determination of plasma volanesorsen concentrations will be collected prior to dosing, and at various times throughout the dosing and post-treatment follow-up period as noted in the tables below.

PK Sampling Schedule (All Patients except PK Subgroup)

Week	**Wk 1**	**Wk 4**	**Wk 8**	**Wk 13**	**Wk 26**	**Wk 38**	**Wk 52**	**Wk 65**
Study Day	**D1**	**D22**	**D50**	**D85**	**D176**	**D260**	**D358**	**D449**
Visit Window +/- Days	0	2	2	2	2	3	2	7
Time Point	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime

PK Sampling Schedule (PK Subgroup only*)

Week	**Wk 1**	**Wk 1**	**Wk 4**	**Wk 8**	**Wk 13**	**Wk 26**	**Wk 38**	**Wk 52**	**Wk 65**
Study Day	**D1**	**D2**	**D22**	**D50**	**D85**	**D176**	**D260**	**D358**	**D449**
Visit Window +/- Days	**0**	**0**	**2**	**2**	**2**	**2**	**3**	**2**	**7**
Time Point	Pre-dose, 1, 2, 3, 4, 6, 8, and 12 hrs post-dose	24 hrs post-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime

* Patients at selected sites will be asked to participate in the extended 24-hour PK profile beginning on Study Day 1. Participation is optional.

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

The following grading recommendations for adverse events relating to lab test abnormalities are based upon the **Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010**

Adverse Event	Mild	Moderate	Severe
Hematology			
aPTT prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage
Eosinophils increased†	650 – 1,500 cell/mm^3	1,501 - 5,000 cell/mm^3	>5,000 cell/mm^3
Fibrinogen decreased	<1.0 - 0.75 x LLN or <25% decrease from baseline	<0.75 - 0.5 x LLN or 25 - <50% decrease from baseline	<0.5 x LLN or ≥50% decrease from baseline
Hemoglobin decreased (Anemia)	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated
Hemoglobin increased	Increase in >0 - 2 g/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 g/dL above ULN or above baseline if baseline is above ULN	Increase in >4 g/dL above ULN or above baseline if baseline is above ULN
INR increased	>1 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation
Lymphocyte count decreased	<LLN - 800/mm^3; <LLN - 0.8 x 10^9/L	<800 - 500/mm^3; <0.8 - 0.5 x 10^9 /L	<500 /mm^3; <0.5 x 10^9 /L
Lymphocyte count increased	-	>4000/mm^3 - 20,000/mm^3	>20,000/mm^3
Neutrophil count decreased	<LLN - 1500/mm^3; <LLN - 1.5 x 10^9 /L	<1500 - 1000/mm^3; <1.5 - 1.0 x 10^9 /L	<1000/mm^3; <1.0 x 10^9 /L
Platelet count decreased	<LLN - 75,000/mm^3; <LLN - 75.0 x 10^9 /L	<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9 /L	<50,000/mm^3; <50.0 x 10^9 /L
White blood cell decreased	<LLN - 3000/mm^3; <LLN - 3.0 x 10^9 /L	<3000 - 2000/mm^3; <3.0 - 2.0 x 10^9 /L	<2000/mm^3; <2.0 x 10^9 /L
Chemistry			
Acidosis	pH <normal, but >=7.3	-	pH <7.3
Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Alkalosis	pH >normal, but ≤7.5	-	pH >7.5
Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 x ULN
Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

Adverse Event	Mild	Moderate	Severe
Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer
CD4 lymphocytes decreased	<LLN - 500/mm^3; <LLN - 0.5 x 10^9 /L	<500 - 200/mm^3; <0.5 - 0.2 x 10^9 /L	<200/mm^3; <0.2 x 10^9 /L
CPK increased*	>ULN - <6 ULN	6 - 10 x ULN	>10 x ULN
Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 x ULN
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 mg/dL; >3.1 mmol/L; Ionized calcium >1.6 mmol/L; hospitalization indicated
Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 mg/dL; >13.9 mmol/L; hospitalization indicated
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0; hospitalization indicated
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 mg/dL; >1.23 mmol/L
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 mmol/L; hospitalization indicated
Hyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 mg/dL; <1.75 mmol/L; Ionized calcium <0.9 mmol/L; hospitalization indicated
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 mg/dL; <3.0 mmol/L	<40 mg/dL (<2.2 mmol/L) AND requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions‡
Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 mmol/L; hospitalization indicated
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 mg/dL; <0.4 mmol/L
Hyponatremia	<LLN - 130 mmol/L	-	<130 mmol/L
Hypophosphatemia	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 mg/dL; <0.6 mmol/L
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

Adverse Event	Mild	Moderate	Severe
Urine			
Proteinuria Adults Children	1+ proteinuria; urinary protein <1.0 g/24 hrs -	2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs; Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Urinary protein ≥3.5 g/24 hrs; Urine P/C >1.9
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated

†Grading for this parameter is derived from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007

*Grading for this parameter is derived from the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0, Nov 2014

‡Modified for consistency with the ADA and Endocrine Society Guidelines (Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. Diabetes Care 2013;36:1384-95)