This Was a Phase 1/2, Double-blind, Randomized, Placebo-controlled, Dose-escalation Study Conducted at a Single Center for the Healthy Volunteer Cohorts in up to 56 Participants. It Consisted of 1 Single-dose Cohort and 3 Multiple-dose Cohorts (n = 12 Per Cohort, 10 Active:2 Placebo). The Open-label, hATTR Patient Cohort Portion of the Study Was Conducted at Multiple Centers.

NCT03728634

06 April 2020

ionispharma.com

2855 Gazelle Court
Carlsbad, CA 92010

(760) 931-9200

Official Title: A Phase 1/2 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of ION-682884, an Antisense Inhibitor of Transthyretin Production, in Healthy Volunteers and Patients with Hereditary Transthyretin-Mediated Amyloidosis

NCT Number: NCT03728634

Document Date: Protocol Amendment Version 2: 12-June-2019

1. STUDY INFORMATION

1.1. Protocol and Protocol Amendments

The protocol was amended 2 times. The latest version of the protocol (Protocol Amendment 2) is provided along with the change summary for the revision.

Protocol Version	Date	Document Provided
Original	05 September 2018	None
Protocol Amendment 1	26 October 2018	None
Protocol Amendment 2	12 June 2019	Protocol and change summary

IONIS PHARMACEUTICALS, INC.

ION-682884-CS1

A Phase 1/2 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of ION-682884, an Antisense Inhibitor of Transthyretin Production, in Healthy Volunteers and Patients with Hereditary Transthyretin-Mediated Amyloidosis

Protocol Amendment 2 – 12 June 2019

Trial Sponsor: Ionis Pharmaceuticals, Inc.
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Sponsor Signatory: [redacted]
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Phone: [redacted]

ION-682884-CS1

A Phase 1/2 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of ION-682884, an Antisense Inhibitor of Transthyretin Production, in Healthy Volunteers and Patients with Hereditary Transthyretin-Mediated Amyloidosis

Protocol Amendment 2 – 12 June 2019

Protocol History:

Original Protocol: 5 September 2018

Protocol Amendment 1: 26 October 2018

Sponsor:

Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010

See electronic signature and date attached at end of document

[redacted], MD
[redacted]

Confidentiality Statement

Protocol Signature Page

Protocol Number: ION-682884-CS1

Protocol Title: A Phase 1/2 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of ION-682884, an Antisense Inhibitor of Transthyretin Production, in Healthy Volunteers and Patients with Hereditary Transthyretin-Mediated Amyloidosis

Amendment: Amendment 2

Date: 12 June 2019

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "A Phase 1/2 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of ION-682884, an antisense inhibitor of Transthyretin Production, in Healthy Volunteers and Patients with Hereditary Transthyretin-Mediated Amyloidosis," dated 12 June 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.

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:	ION-682884-CS1
Protocol Title:	A Phase 1/2 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of ION-682884, an Antisense Inhibitor of Transthyretin Production, in Healthy Volunteers and Patients with Hereditary Transthyretin-Mediated Amyloidosis
Amendment Number:	2
Amendment Date:	12 June 2019

Following a review of the data from the completed treatment period of the planned healthy volunteer portion of this study (Cohorts A, B and C), the Sponsor intends to run an additional multiple-dose cohort to better assess the safety, tolerability, pharmacokinetics and pharmacodynamics of ION-682884.

Protocol ION-682884-CS1 already contained a provision for an additional healthy volunteer cohort, Cohort E, to be enrolled and dosed at ≤ 120 mg per dose using the same dosing schedule as the other 2 multiple-dose, healthy volunteer cohorts (Cohorts A and B).

The purpose of this amendment is to confirm the Sponsor's intent to perform Cohort E and to identify the intermediate dose level of 60 mg per dose throughout the protocol for this cohort.

PROTOCOL SYNOPSIS

Protocol Title	A Phase 1/2 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of ION-682884, an Antisense Inhibitor of Transthyretin Production, in Healthy Volunteers and Patients with Hereditary Transthyretin-Mediated Amyloidosis
Study Phase	1/2
Indication	Hereditary Transthyretin-Mediated Amyloidosis (hATTR)
Primary Objectives	To evaluate the safety and tolerability of single and multiple doses of ION-682884 administered subcutaneously (SC) to healthy volunteers and patients with hATTR.
Secondary Objectives	To evaluate the pharmacokinetic and pharmacodynamic profiles of single and multiple doses of ION-682884 administered subcutaneously to healthy volunteers and patients with hATTR.
Exploratory Objectives	To evaluate the effects of ION-682884 subcutaneous injection on the mNIS+7, Norfolk QoL, 6MWT, 10MWT, EQ-5d, SF-36, COMPASS, and Amyloidosis-specific QoL.
Study Design	**Healthy Volunteers (Cohorts A, B, C and E)** Blinded, placebo-controlled, dose-escalation, single-center study For each dose cohort, the first 2 sentinel subjects will be dosed on the same day. If no major safety concerns are observed following 48 hours of observation, as determined by the Safety Committee, (comprised of the Investigator, the Sponsor Medical Monitor and an Independent Safety Monitor), dosing of the remaining subjects in that cohort may proceed. **hATTR Patients (Cohort D)** Open-label, multi-center study. At the end of the Treatment Period, eligible patients may elect to enroll in an open-label extension (OLE) study pending study approval by the IRB/IEC and the appropriate regulatory authority. Patients not participating in the OLE will enter the 13-week Post-Treatment evaluation portion of this study.
Number of Subjects	**Healthy Volunteers (Cohorts A, B, C and E)** Approximately 36 healthy volunteers are planned to be enrolled in the study. Additional subjects may be added to better assess the safety, tolerability, pharmacokinetic and pharmacodynamic of ION-682884 to meet study objectives. Maximum enrollment of healthy volunteers will be limited to 60 subjects. **hATTR Patients (Cohort D)** Approximately 20 hATTR patients are planned to be enrolled in the study. Additional patients may be added to better assess the safety, tolerability, pharmacokinetic and pharmacodynamic of ION-682884 to meet study objectives. Maximum enrollment will be limited to 30 hATTR patients.
Study Population	**Inclusion Criteria for Healthy Volunteers (Cohorts A, B, C and E)** 1. Must have given written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements 2. Healthy males or females of non-childbearing potential, aged 18 to 65 inclusive at the time of informed consent.

PROTOCOL SYNOPSIS *Continued*

Study Population ***Continued***	**Inclusion Criteria for Healthy Volunteers (Cohorts A, B, C and E)** ***Continued*** 3. Females must be non-pregnant and non-lactating, and either surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or post-menopausal (defined as 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved. Males must be surgically sterile or abstinent*, if engaged in sexual relations with a female of child-bearing potential, the subject must be using an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 91 days (single-dose cohorts) or 13 weeks (multiple-dose cohorts) after the last dose of Study Drug (ION-682884 or placebo) *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. 4. Willing to refrain from strenuous exercise/activity (for example heavy lifting, weight training, intense aerobics classes etc.) for at least 72 hours prior to study visits 5. Weight ≥ 50 kg and body mass index (BMI) < 32 kg/m^2 6. Willingness to take vitamin A supplements **Exclusion Criteria for Healthy Volunteers (Cohorts A, B, C and E)** 1. Clinically-significant abnormalities in medical history (e.g., previous acute coronary syndrome within 6 months of Screening, major surgery within 3 months of Screening) or physical examination 2. Screening laboratory results as follows, or any other clinically-significant abnormalities in screening laboratory values that would render a subject unsuitable for inclusion • Random spot urine protein/creatinine (P/C) ratio (UPCR) ≥ 200 mg/g. In the event of P/C ratio (UPCR) above this threshold eligibility may be confirmed by a repeat random spot UPCR ≥ 200 mg/g or a 24-hr urine ≥ 200 mg/24 hr • Positive test (including trace) for blood on urinalysis. In the event of a positive test eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field • ALT, AST, bilirubin, alkaline phosphatase, serum creatinine, BUN > upper limit of normal (ULN) • Fasting blood glucose > ULN • Platelet count < lower limit of normal (LLN) 3. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1 4. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator 5. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B 6. Uncontrolled hypertension (blood pressure [BP] > 160/100 mm Hg)

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	**Exclusion Criteria for Healthy Volunteers (Cohorts A, B, C and E) *Continued*** 7. 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 8. Treatment with another investigational drug, biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever is longer 9. Previous treatment with an oligonucleotide or other RNA therapeutic (including siRNA) within 4 months of Screening if single-dose received, or within 12 months of Screening if multiple doses received 10. History of bleeding diathesis or coagulopathy 11. Regular use of alcohol within 6 months prior to screening (> 7 drinks/wk for females, > 14 drinks/wk for males (1 drink = 5 ounces (150 mL) of wine or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of hard liquor), or use of soft drugs (such as marijuana) within 3 months prior to screening, or hard drugs (such as cocaine and phencyclidine) within 1 year prior to screening, or positive urine drug screen at Screening 12. Concomitant medication restrictions including over-the-counter and herbal remedies, other than occasional acetaminophen (paracetamol) or ibuprofen unless authorized by the Sponsor Medical Monitor 13. Use of oral anticoagulants, unless the dose has been stable for 4 weeks prior to the first dose of Study Drug (ION-682884 or placebo) and regular clinical monitoring is performed 14. Smoking limitations: smoking >10 cigarettes a day 15. Blood donation of 50 to 499 mL within 30 days of Screening or of > 499 mL within 60 days of Screening 16. Have any other conditions, which, in the opinion of the Investigator or Sponsor would make the subject unsuitable for inclusion, or could interfere with the subject participating in or completing the Study **Inclusion Criteria for hATTR Patients (Cohort D)** To be eligible to participate in this study cohort candidates must meet the following eligibility criteria within 6 weeks of Study Day 1, or at the time point specified in the individual eligibility criterion listed. 1. Must have given written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements 2. Aged 18 to 82 years at the time of informed consent 3. Females must be non-pregnant and non-lactating, and either surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or post-menopausal (defined as 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved. Males must be surgically sterile or abstinent*, if engaged in sexual relations with a female of child-bearing potential, the subject must be using an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 13 weeks after the last dose of ION-682884

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	**Inclusion Criteria for hATTR Patients (Cohort D) *Continued*** *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. 4. hATTR-PN as defined by: a. Polyneuropathy Disability (PND) Stage I-III b. Documented genetic mutation in the TTR gene c. Symptoms consistent with polyneuropathy as measured by NIS score ≥ 10 d. Willingness to take vitamin A supplements 5. BMI > 16 kg/m^2 **Exclusion Criteria for hATTR Patients (Cohort D)** 1. Clinically-significant abnormalities in medical history (e.g., previous acute coronary syndrome or major surgery within 3 months of Screening) or physical examination 2. Screening laboratory results as follows, or any other clinically-significant abnormalities in screening laboratory values that would render a subject unsuitable for inclusion a. ALT/AST > 1.9 x ULN b. Bilirubin ≥ 1.5 x ULN (patients with bilirubin ≥ 1.5 x ULN may be allowed on study following discussion with the Study Medical Monitor if indirect bilirubin only is elevated, ALT/AST is not greater than the ULN and genetic testing confirming Gilbert's disease) c. Platelets < 125 x 10^9/L d. Urine protein/creatinine (P/C) ratio (UPCR) ≥ 1000 mg/g. In the event of P/C ratio (UPCR) above this threshold eligibility may be confirmed by by a repeat random spot UPCR ≥ 1000 mg/g or a 24-hr urine ≥ 1000 mg/24 hr e. Renal insufficiency as defined by estimated creatinine clearance calculated according to the formula of CKD-EPI < 45 mL/min/ 1.73 m^2 at Screen. If the calculated creatinine clearance is thought to be artificially low, a 24-hr urine creatinine clearance can be completed with prior Sponsor approval f. TSH values outside normal range (unless approved by the Study Medical Monitor) 3. Serum retinol level at Screen < LLN For patients with a TTR mutation at position 84 (e.g., Ile84Ser or Ile84Asn) and retinol < LLN the exclusion criterion is signs or symptoms of vitamin A deficiency (such as dry eye, bitots' spot observed in the ophthalmology exam, that in the opinion of the ophthalmologist is consistent with vitamin A deficiency) 4. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1 5. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator 6. Known history of or positive test for HIV, hepatitis C or chronic hepatitis B

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	**Exclusion Criteria for hATTR Patients (Cohort D) *Continued*** 7. Uncontrolled hypertension (BP > 160/100 mm Hg) 8. 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. Patients with a history of other malignancies that have been treated with curative intent and which have no recurrence within 5 years may also be eligible if approved by the Sponsor Medical Monitor 9. Treatment with another investigational drug, biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever is longer. Does not apply to tafamidis, diflunisal, doxycycline or TUCA if subject has been on a stable dose of drug for ≥ 4 weeks and continues receiving the same dose for the duration of the study 10. Previous treatment with an oligonucleotide or other RNA therapeutic (including siRNA) within 3 months of Screening 11. Karnofsky performance status ≤ 50 12. Diagnosis of type 1 or type 2 diabetes for equal or more than 5 years; Screening HbA1c > 9.5%; or history of severe peripheral neuropathy due to diabetes 13. Other causes of sensorimotor or autonomic neuropathy (e.g., autoimmune disease) 14. Prior liver transplant or anticipated liver transplant within 1 year of Screening 15. New York Heart Association (NYHA) functional classification of ≥ 3 16. NT-proBNP > 3000 pg/mL 17. Known Primary Amyloidosis (AL amyloidosis) 18. Known Leptomeningeal Amyloidosis 19. Known Multiple Myeloma 20. Monoclonal gammopathy of undetermined significance (MGUS) unless serum M protein level of < 3 g/dL, < 10% clonal plasma cells in the bone marrow, urine monoclonal protein < 500 mg/24 hrs and no evidence of end-organ damage 21. Have any other conditions, which, in the opinion of the Investigator or Sponsor would make the subject unsuitable for inclusion, or could interfere with the subject participating in or completing the Study
Treatment Groups	**Healthy Volunteers (Cohorts A, B, C and E)** There are 3 planned cohorts in healthy volunteers, 2 multiple-dose cohorts (Cohorts A and B) and 1 single-dose cohort (Cohort C) and 1 additional multiple-dose cohort (Cohort E). Cohorts A, B, C and E are comprised of 12 subjects, randomized 10:2, active:placebo. Subjects in the multiple-dose cohorts will receive SC doses of Study Drug once every 4 weeks for a total of 12 weeks (total of 4 doses). Subjects in the single-dose cohort will receive 1 SC dose of Study Drug on Day 1. For each dose cohort, the first 2 (sentinel) subjects (randomized 1 active:1 placebo) will be dosed on the same day. If no major safety concerns are observed following 48 hours of observation, as determined by the Safety Committee, dosing of the remaining 10 subjects (randomized 9 active:1 placebo) in that cohort may proceed.

PROTOCOL SYNOPSIS *Continued*

<table>
<tr><td>Treatment Groups Continued</td><td>
<u>Healthy Volunteers (Cohorts A, B, C and E) Continued</u>
Following the administration of the 1st dose of Study Drug in each multiple-dose cohort, individual subjects must have completed their Day 15 safety evaluations with an acceptable safety profile, as determined by the Safety Committee, before receiving additional doses of Study Drug.
<table>
<tr><th>Cohort</th><th>Number of Doses</th><th>Total ION-682884</th></tr>
<tr><td>Cohort A: 45 mg ION-682884 or placebo</td><td>4</td><td>180 mg</td></tr>
<tr><td>Cohort B: 90 mg ION-682884 or placebo</td><td>4</td><td>360 mg</td></tr>
<tr><td>Cohort C: 120 mg ION-682884 or placebo</td><td>1</td><td>120 mg</td></tr>
<tr><td>Cohort E: 60 mg ION-682884 or placebo</td><td>4</td><td>240 mg</td></tr>
</table>
The additional multiple-dose, healthy-volunteer cohort with 4 once-every-4-week doses of 60 mg ION-682884 or placebo, was added to further elucidate safety or PD effects of ION-682884.
<u>hATTR Patients (Cohort D)</u>
There is 1 planned, open-label, multiple-dose cohort (Cohort D) comprised of up to 20 patients with hATTR. Patients in this cohort will receive SC doses of ION-682884 once every 4 weeks for a total of 12 weeks (total of 4 doses). The dose level in this cohort will not exceed doses planned for Healthy Volunteers (120 mg) and will be selected after reviewing the safety and pharmacodynamic data obtained in the healthy volunteer portion of this study.
Following the administration of the 1st dose of ION-682884 patients must have completed their Day 15 safety evaluations with an acceptable safety profile, as determined by the Safety Committee, before receiving additional doses of Study Drug.
<table>
<tr><th>Cohort</th><th>Number of Doses</th><th>Total ION-682884</th></tr>
<tr><td>Cohort D: ≤ 120 mg ION-682884</td><td>4</td><td>≤ 480 mg</td></tr>
</table>
</td></tr>
<tr><td>Study Drug Dosage and Administration</td><td>The Sponsor will provide ION-682884 (150 mg/mL, 0.8 mL) and the site will provide Placebo (0.9% sterile saline). All doses will be given by SC injection.</td></tr>
<tr><td>Dose Escalation</td><td>
<u>Healthy Volunteers (Cohorts A and B)</u>
Dosing of Cohort B (4 x 90 mg ION-682884 or placebo) can only proceed when at least 8 subjects in Cohort A have completed Day 29 safety evaluations and have demonstrated an acceptable safety profile as determined by the Safety Committee.
<u>Healthy Volunteers (Cohorts C)</u>
Dosing of Cohort C (1 x 120 mg ION-682884 or placebo) can only proceed when at least 8 subjects in Cohort A have completed Day 57 safety evaluations and have demonstrated an acceptable safety profile as determined by the Safety Committee.
<u>Additional Multiple-Dose Cohort in Healthy Volunteers (Cohort E)</u>
Dosing of the additional multiple-dose cohort (4 x 60 mg ION-682884 or placebo), can only proceed when at least 8 subjects in Cohort B have completed Day 29 safety evaluations and have demonstrated an acceptable safety profile as determined by the Safety Committee.
</td></tr>
</table>

PROTOCOL SYNOPSIS *Continued*

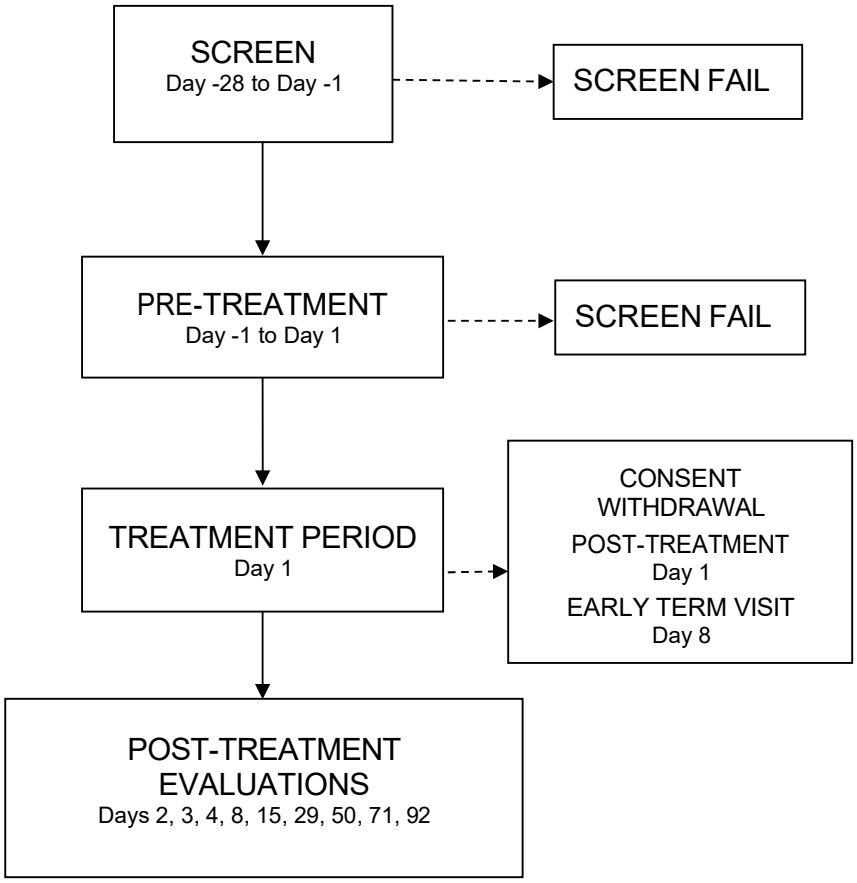
Dose Escalation *Continued*	**hATTR Patients (Cohort D)** Enrollment in Cohort D (4 x ≤ 120 mg ION-682884) can only proceed when at least 8 subjects in Cohort B (4 x 90 mg ION-682884 or placebo) have completed the Treatment Period and have demonstrated an acceptable safety profile as determined by the Principal Investigator and the Safety Committee. The dose level for Cohort D will be informed by safety and PD data from the multiple-dose and single-dose healthy-volunteer cohorts. **Cohorts (A, B, C and E)** Based on the judgement of the Principal Investigator and the Sponsor Medical Monitor, any cohort may be expanded to enroll additional subjects (no more than 2 times the original size) and/or additional single-dose and/or multiple-dose cohorts at intermediate dose(s) may be added to better assess the safety, tolerability, or pharmacodynamic profile of ION-682884.
Rationale for Dose and Schedule Selection	A starting dose of 45 mg (approximately 0.6 mg/kg/month body weight in a 70-kg subject) was selected based on approximately 37-fold safety margin and expectation of total body weight-based dose scaling between monkeys and humans, where no drug-related toxicologically significant findings were observed up to 6 mg/kg/wk (24 mg/kg/month equivalent exposure) after 13 weeks of treatment in monkeys. The dose of 90 mg will provide an 18-fold safety margin.
Adjustment of Dose and/or Treatment Schedule	Adjustment of dose and/or schedule is not permitted
Study Visit Schedule and Procedures	Detailed Information regarding the study procedures are outlined in Section 6 and Appendices A, B, C, and D. Blood and urine samples will be collected regularly throughout the study for safety, pharmacokinetic, and pharmacodynamics analysis. Appendix B shows a list of analytes required for the study. The safety of ION-682884 will be monitored in an ongoing fashion during the study. **Single-Dose Cohort C** The length of each subject's participation in Cohort C is approximately 17 weeks from screening to last study visit. There are 2 overnight stays in the clinic (Days -1 and 1). On Day 1, subjects will receive a single SC dose of Study Drug. **Multiple-Dose Cohorts A, B and E** The length of each subject's participation in Cohorts A, B and E is approximately 29 weeks, including a 4-week Screening Period, a 12-week Treatment Period, and a 13-week Post-Treatment Evaluation Period. There are 3 overnight stays in the clinic (Days -1, 1 and 85). Subjects will receive a total of 4, once every 4 weeks, fixed SC doses of Study Drug. **Multiple-Dose Cohort D** The length of each subject's participation in Cohort D is approximately 29 weeks, including a 4-week Screening Period, a 12-week Treatment Period, and a 13-week Post-Treatment Evaluation Period. There is 1 overnight stay in the clinic (Days -1). Subjects will receive a total of 4, once every 4 weeks, fixed SC doses of ION-682884.

PROTOCOL SYNOPSIS *Continued*

Study Visit Schedule and Procedures *Continued*	At the end of the Treatment Period, eligible patients may elect to enroll in an OLE study pending study approval by the IRB/IEC and the appropriate regulatory authority. Patients not participating in the OLE will enter the 13-week Post-Treatment Evaluation portion of this study unless consent is withdrawn.
Primary Endpoints	Analysis of safety labs, AEs, concomitant medications, ECG and physical examinations of healthy volunteers and patients with TTR amyloidosis following subcutaneously administration of single and/or multiple doses of ION-682884.
Secondary Endpoints	Analysis of pharmacokinetic data (plasma PK and urinary excretion) and pharmacodynamic data (TTR and RBP4 knockdown) in healthy volunteers and patients with TTR amyloidosis following subcutaneous administration of single and/or multiple doses of ION-682884.
Additional/Exploratory Endpoints	Exploratory endpoints for the open-label, hATTR patient cohort are the change from Baseline to Week 15 in the: • Norfolk QOL-DN questionnaire total score • 6MWT • 10MWT • EQ-5d • SF-36 questionnaire domain scores • COMPASS-31 questionnaire • Amyloidosis-specific QoL questionnaire
Statistical Considerations	There is no statistical rationale for the selected sample size of the healthy volunteer, single- and multiple-dose treatment cohorts. The sample size was based on prior experience to ensure that the safety and tolerability of ION-682884 will be adequately assessed while minimizing unnecessary subject exposure. Unblinded analyses may be conducted after completion of dosing for the single-dose and each multiple-dose cohort.
Sponsor	Ionis Pharmaceuticals, Inc.

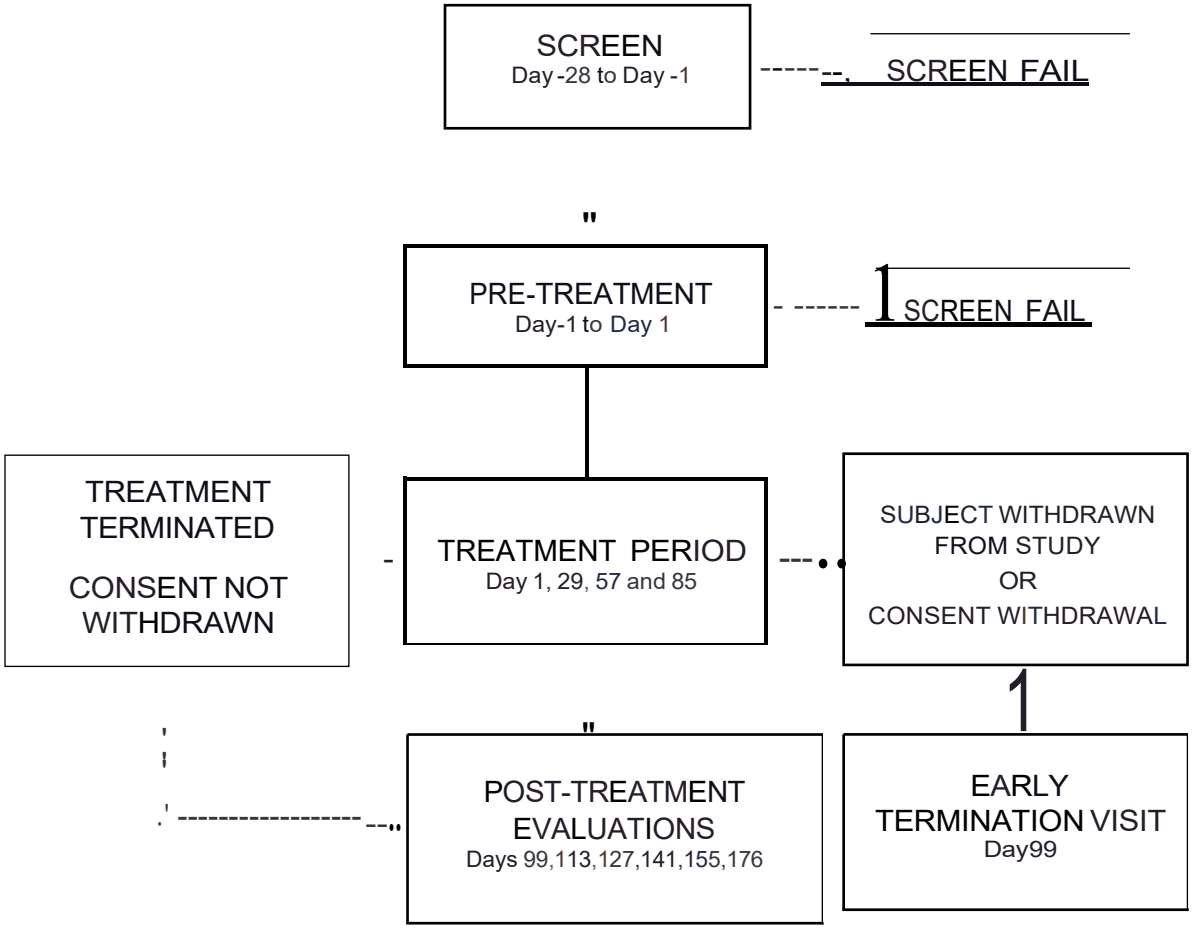
STUDY DESIGN AND TREATMENT SCHEMA

Schema for Single-Dose Cohort C



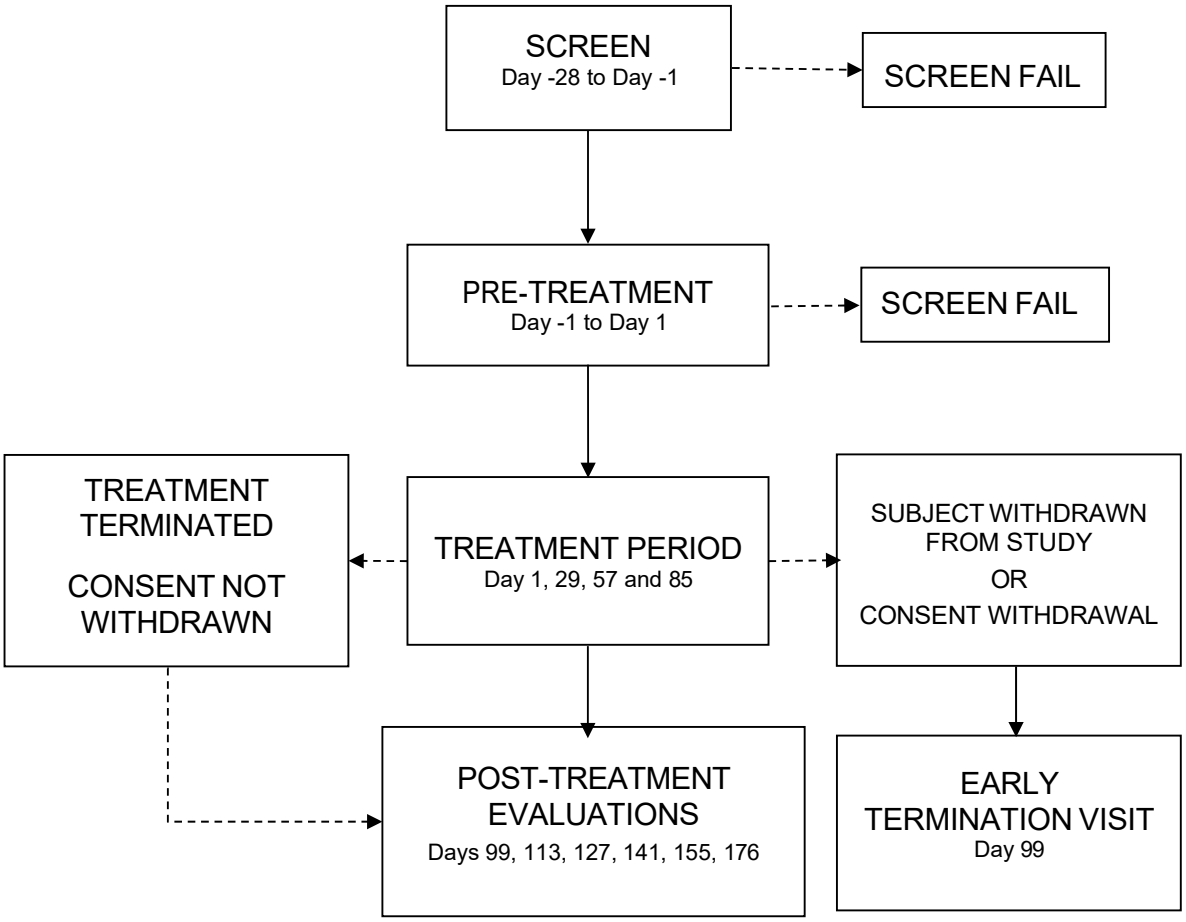
STUDY DESIGN AND TREATMENT SCHEMA *Continued*

Schema for Every 4 Week, Multiple-Dose Cohorts (A, B and E)



STUDY DESIGN AND TREATMENT SCHEMA *Continued*

Schema for Every 4 Week, Multiple-Dose Cohort D



STUDY GLOSSARY

Abbreviation	Definition
+7	Sum 7 test. Includes measurements of nerve conduction, vibration threshold and heart rate to deep breathing
Alb/C ratio	albumin/creatinine ratio (performed on urine sample)
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
AUC	area under the curve
BP	blood pressure
BMI	body mass index
CKMB	creatine kinase-muscle/brain
CM	cardiomyopathy
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
ECHO	echocardiogram
EOT	end-of-treatment
ERG	electroretinogram
ET	early termination
GLS	global longitudinal strain
hATTR	hereditary transthyretin amyloidosis
hATTR-PN	hATTR with polyneuropathy
hATTR-CM	hATTR with cardiomyopathy
HIV	human immunodeficiency virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IXRS	interactive voice/web-response system
LLN	lower limit of normal
mBMI	modified body mass index (requires determination of plasma albumin levels; mBMI = BMI x serum albumin g/L)
MGUS	monoclonal gammopathy of undetermined significance
MMRM model	mixed effect model with repeated measures

mNIS+7	modified neuropathy impairment score +7. Standard NIS but with modifications made to the +7 component
Modified +7	+7 test with modifications made to the sensory and nerve conduction testing
MPV	mean platelet volume
NIS	neuropathy impairment score
NIS-LL	neuropathy impairment score-lower limb
NOAEL	No Observable Adverse Effect Level
Norfolk QOL-DN	Norfolk quality of life-diabetic neuropathy questionnaire
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
OLE	open label extension
OLT	orthotopic liver transplantation
P/C ratio	protein/creatinine ratio (performed on urine sample)
PD	pharmacodynamic
PK	pharmacokinetic
PND	polyneuropathy disability
PND Score	polyneuropathy disability score
RDA	recommended daily allowance
RBP4	retinol binding protein 4
SAE	serious adverse event
SAP	statistical analysis plan
SC	Subcutaneous(ly)
Study Day 1	defined as the first day Study Drug is administered to the patient
Study Drug	ION-682884 or placebo
SUSARs	suspected unexpected serious adverse reactions
TTR	transthyretin
TUCA	tauroursodeoxycholic acid
ION-682884	antisense inhibitor of TTR
ULN	upper limit of normal
UPCR	urine protein/creatinine ratio
UTR	untranslated region
WOCBP	woman of child-bearing potential

1. OBJECTIVES AND ENDPOINTS

1.1 Objectives

1.1.1 Primary Objectives

To evaluate the safety and tolerability of single and multiple doses of ION-682884 administered subcutaneously to healthy volunteers and patients with hATTR.

1.1.2 Secondary Objectives

To evaluate the pharmacokinetic and pharmacodynamic profiles of single and multiple doses of ION-682884 administered subcutaneously to healthy volunteers and patients with hATTR.

1.1.3 Exploratory Objectives

To evaluate the effects in hATTR patients of multiple doses of ION-682884 on the mNIS+7, Norfolk QoL, 6MWT, 10MWT, EQ-5d, SF-36, COMPASS, and Amyloidosis-specific QoL.

1.2 Study Endpoints

1.2.1 Primary Endpoints

Analysis of safety labs, AEs, concomitant medications, ECG and physical examinations of healthy volunteers and patients with TTR amyloidosis following subcutaneously administration of single and/or multiple doses of ION-682884.

1.2.2 Secondary Endpoints

Analysis of pharmacokinetic data (plasma PK and urinary excretion) and pharmacodynamic data (TTR and RBP4 reduction) in healthy volunteers and patients with TTR amyloidosis following subcutaneous administration of single and/or multiple doses of ION-682884. Metabolite identification and profiling may be determined in select plasma, urine, and fecal samples.

Analysis of pharmacodynamic data will determine the change and percent change from Baseline in plasma TTR and RBP4 levels following single- and multiple-dose SC administration of Study Drug.

1.2.3 Additional/Exploratory Endpoints

Exploratory endpoints for the open-label, hATTR patient cohort are the change from Baseline to Week 15 in the:

- mNIS +7 score
- Norfolk QOL-DN questionnaire total score
- 6MWT
- 10MWT
- EQ-5d
- SF-36 questionnaire domain scores
- COMPASS-31 questionnaire
- Amyloidosis-specific QoL questionnaire

2. BACKGROUND AND RATIONALE

2.1 Overview of Disease

2.1.1 Disease Background

Hereditary transthyretin amyloidosis (hATTR) is a progressive, irreversible, and fatal disease. Average life expectancy is 3 to 15 years after diagnosis (Gertz 2017; FDA Guidance for Industry 2005) (pgs 8-9). Patients typically die due to malnutrition and cachexia, renal failure, and cardiac disease (Coelho et al. 2008). Hereditary transthyretin amyloidosis is caused by mutations in the gene that codes for TTR, a carrier protein for thyroxine and vitamin A. Single-point gene mutations destabilize the normal tetrameric structure of the TTR protein, causing its dissociation into free monomers. These monomers misfold and subsequently aggregate into insoluble, extracellular fibril deposits, causing cell degeneration and death (Quintas et al. 2001; Plante-Bordeneuve and Said 2011).

Aggregation of wild-type transthyretin is also seen to cause lethal disease. Though clinically-insignificant amounts of wild-type transthyretin-derived amyloid deposits are routinely detected in histological analysis of ventricles in 50% to 80% of patients > 80 years, massive accumulation of wild-type transthyretin leads to progressive congestive heart failure referred to as wildtype ATTR amyloidosis (wtATTR). Prevalence of wtATTR increases with advancing age and is overwhelmingly diagnosed in men aged > 70 years (Ng et al. 2005; Falk 2011). The mechanism by which wild-type transthyretin accumulates in the heart with increasing age remains unclear.

In contrast to wtATTR in which amyloid deposits are found primarily in the heart, accumulation of amyloid deposits in hATTR occur in multiple organ systems, particularly the nervous system, gastrointestinal tract, kidney, and heart. Due to the multiple organ deposition of amyloid, the disease has a wide clinical spectrum. The phenotypic presentation of the disease is dependent on the pattern of organ involvement. However, historically, hATTR has been divided into 2 major phenotypes: Hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN), when the peripheral nerves and gastrointestinal tract are predominantly involved, and hATTR with cardiomyopathy (hATTR-CM), when the heart is predominantly involved.

The worldwide prevalence of hATTR-PN has been estimated at approximately 10,000 patients (Coelho et al. 2008). The main clinical manifestations of hATTR-PN are progressive peripheral sensorimotor and autonomic neuropathy (Plante-Bordeneuve and Said 2011). Non-specific and symmetrical numbness, pain, and temperature sensitivity typically begin in the lower extremities, progressing distal to proximal. Motor neuropathy follows within a few years, which affects ambulatory status (Coutinho et al. 1980; Sekijima et al. 2009; Plante-Bordeneuve and Said 2011). Hereditary ATTR-PN is classified into 3 stages based on ambulatory status (Coutinho et al. 1980): Stage 1 does not require assistance with ambulation, Stage 2 requires assistance with ambulation, and Stage 3 is wheelchair bound. This staging system was used to classify severity of disease in patients being considered for enrollment in the pivotal study of ISIS 420915 (CS2). Disease severity can also be assessed using the Polyneuropathy Disability (PND) score, which is a 5-stage scoring system (Suhr et al. 1996).

Life-threatening autonomic dysfunction develops in many patients, affecting the cardiocirculatory, gastrointestinal, and genitourinary systems. Symptoms include orthostatic hypotension, which can lead to dizziness and frequent falls. Gastrointestinal symptoms include diarrhea, severe constipation, alternating diarrhea/constipation, vomiting, and gastroparesis, all leading to progressive weight loss. Urinary symptoms, fecal incontinence, and, in men, erectile dysfunction may be present (Plante-Bordeneuve and Said 2011).

Cardiac involvement has been estimated to occur in 80% of transthyretin amyloidosis (Plante-Bordeneuve and Said 2011). The age of onset in patients is between 60 and 70 years and the mean life expectancy from symptom onset is 5–6 years. In patients with hATTR-CM, mutant TTR amyloid fibrils infiltrate the myocardium, with resultant diastolic dysfunction progressing to restrictive cardiomyopathy and heart failure (Castano et al. 2015). Conduction abnormalities and arrhythmias are also common, and many patients require pacemaker and/or defibrillator insertion. Presence of significant cardiomyopathy is associated with poorer prognosis.

Amyloid deposits in the kidney are common and can result in microalbuminuria with progression to renal failure in a subset of patients. Symptoms of chronic kidney disease may include lower extremity edema, anemia, fatigue and weakness, and decrease in appetite.

As expected, given the severity of hATTR, there is a significant impact on patients' and caregivers' QoL (Gertz 2017; Stewart et al. 2013). Caregivers have moderate to high levels of fatigue and spend a significant amount of time caring for patients. Hereditary ATTR is associated with a substantial disruption in employment rates and work productivity. There is also a large mental health burden on both caregivers and patients.

2.1.2 Overview of Target – Transthyretin

The name TTR is derived from transporter of thyroxine and retinol and was formerly known as prealbumin. The human TTR gene is over 7 kb in length, has 4 exons, and is found on chromosome 18q2.1. It is synthesized primarily in the liver and, to a lesser extent, by the choroid plexus and retina. It is secreted as a tetramer by the liver into the plasma as a 55 KD protein composed of 4 identical subunits of 14 KD each. A major function of TTR in the plasma is to transport retinol (vitamin A) to tissues through the association with retinol binding protein 4 (RBP4). Retinol is the major circulating form of vitamin A. About 70% of total body retinol is stored in the liver and mobilized into the blood stream bound to RBP4 (D'Ambrosio et al. 2011). The retinol-RBP4 complex in turn binds to TTR, which prevents the complex from being excreted through the kidney. The ratio RBP4:TTR in plasma is around 0.3 in healthy individuals, indicating that most of the circulating TTR remains free of RBP4 ligand (Buxbaum and Reixach 2009). Besides transporting the retinol-RBP4 complex, TTR also transports ~15% of plasma thyroxine with the majority of thyroxine transported by either thyroxine binding globulin or albumin. Recent evidence has suggested that TTR may also have a neuroprotective function in the brain. Brain TTR is produced primarily by the choroid plexus and has been proposed to help with nerve regeneration and to play a protective role in the Alzheimer's disease (Buxbaum and Reixach 2009; Fleming et al. 2009)

It has been demonstrated that mice treated systemically with a TTR-specific ASO had decreased hepatic TTR mRNA levels and serum TTR levels but did not show changes in the expression of TTR in the choroid plexus (Benson et al. 2006; Benson et al. 2017).

2.1.3 Current Therapies

Current therapeutic strategies to treat hATTR include orthotopic liver transplant (OLT) or pharmacotherapy with tafamidis or off-label use of diflunisal, both of which are TTR stabilizers that work by preventing dissociation of the tetramer into amyloid-forming monomers (Adams et al. 2016). Because most of the amyloidogenic-mutated TTR is secreted by the liver, OLT results in rapid disappearance of mutant TTR protein from the serum. However, wild-type TTR protein continues to be produced by the donor liver and can deposit in the pre-existing amyloid deposits in the tissues after transplantation, leading to continual disease progression and, in some cases, accelerating heart disease (Yazaki et al. 2000; Liepnieks and Benson 2007; Yazaki et al. 2007; Liepnieks et al. 2010). Younger patients with early disease, Val30Met (V30M) mutation, and mild symptoms (typically Stage 1) generally experience better outcomes with OLT. Stage 2 patients are often not candidates for OLT due to advanced age, cardiac involvement, or other health reasons (Herlenius et al. 2004; Stangou and Hawkins 2004).

In regard to currently-approved therapies, Onpattro (patisiran), a double-stranded small interfering RNA (siRNA) product which also works by inhibiting production of TTR protein, is approved in the United States for the treatment of the polyneuropathy of hATTR in adults. This drug is given IV every 3 weeks after patients are premedicated with high dose dexamethasone. Tegsedi (inotersen sodium) is authorized in the European Union, the US and Canada for the treatment of Stage 1 or Stage 2 polyneuropathy in adult patients with hATTR. Vyndaqel (tafamidis) is indicated for the treatment of ATTR in adult patients with Stage 1 symptomatic polyneuropathy to delay peripheral neurological impairment, and is currently approved for use in Europe, Japan, and several other countries. In some countries, tafamidis is also indicated for patients with more advanced stages of disease (Stage 2 and/or Stage 3). Diflunisal is a NSAID that is not currently approved for the treatment of hATTR. Off-label use has been reported in patients with Stage 1 and Stage 2 disease (Adams et al. 2016); however, the known cardiovascular and renal side effects associated with the NSAID drug class may limit the use of this drug in older patients with hATTR-PN or patients with hATTR CM.

Consequently, there continues to be an unmet medical need for effective, well-tolerated and convenient treatments that do not require additional premedication for patients with ATTR (both hereditary and wild type) worldwide.

2.2 Therapeutic Rationale

ION-682884 is an antisense drug targeted to human *TTR* mRNA and its hybridization to the cognate TTR mRNA results in the RNase H-mediated degradation of the TTR mRNA, thus preventing production of the TTR protein (see Section 2.3). The strategy of treating hATTR patients with ION-682884 is to reduce the levels of mutated and wild-type TTR protein secreted by the liver, a primary organ for antisense oligonucleotide (ASO) distribution after systemic delivery. It should be noted that ASOs are highly charged hydrophilic molecules that do not cross the blood brain barrier (Levin et al. 2008) and thus systemic treatment with ION-682884 is not predicted to decrease levels of TTR in the brain. It is predicted that decreasing the amount of

liver-derived TTR protein circulating in the plasma by treatment with ION-682884 will result in a decrease in the formation of TTR amyloid fibril deposits, and thus slow or halt disease progression. This strategy is a similar strategy to OLT, with the exception that ION-682884 reduces wild-type protein in addition to the mutated protein. Given that wild-type TTR can continue to deposit as amyloid after liver transplant, this distinction may represent a therapeutic advantage.

Clinical trials in patients with hATTR-PN have used the Neuropathy Impairment Score (NIS), or derivatives of this score such as the NIS Lower Limb (NIS-LL) or the NIS +7, to assess progression of neuropathy. The NIS score was originally developed for assessment of diabetic neuropathy and is a quantitative score of motor, sensory, and reflex function as judged by the clinician (Dyck et al. 1991). The NIS-LL is a subset of the full NIS and evaluates changes in motor, sensory and reflex activity specifically in the lower limbs whereas the full NIS also evaluates changes in the upper limbs and cranial nerves. The NIS or NIS-LL scores are sometimes combined with the Sum 7 Test (or +7) to give the NIS+7 or NIS-LL+7 composite score (Dyck et al. 1997). The +7 Test is an objective score of large fiber function that includes measurements of nerve conduction, vibration threshold and heart rate to deep breathing (an assessment of autonomic function). Thus, the NIS+7 and NIS-LL+7 scores have the advantage of combining a subjective assessment scored by the clinician with objective measurements of autonomic and sensory nerve function, which are both affected in patients with hATTR-PN. The NIS-LL / NIS-LL+7 score is most appropriate to measure neuropathy progression in early Stage 1 hATTR-PN patients. But patients in later Stage 1 and Stage 2 (as is the case for this protocol) can reach a ceiling effect on the NIS-LL score, and therefore the full NIS /NIS+7 is a more appropriate score for these patients. However, even the NIS+7 may not be optimally sensitive for assessment of progression of neuropathy in the target population of this study because it is primarily focused on motor function and on large nerve fibers whereas hATTR-PN has a significant sensory component and affects both large and small nerve fibers, with a great deal of heterogeneity amongst patients in regard to which nerve fiber types are affected (Plante-Bordeneuve et al. 2007). Therefore, in this study, progression of neuropathy will be assessed using a modified NIS +7 score (mNIS +7), which includes a greater sensory component and assesses both large and small nerve fiber function. During the mNIS+7 assessment, the standard NIS+7 assessment will also be collected and the NIS+7 will be analyzed as a secondary endpoint. The NIS score will be used for selection of the target population (inclusion criteria) because there is a greater body of data correlating NIS score with stage of disease.

The Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) questionnaire is included to assess disease specific changes in the patients' perceived quality of life. This instrument is a nerve fiber-specific, 5-domain tool that has been validated in hATTR-PN patients (Vinik et al. 2011). In addition, the SF-36 questionnaire is included as a non-disease specific tool to assess the patient's perceived functional health and well-being.

Many patients with hATTR-PN also have hATTR-CM. There is no widely-accepted method for measuring progression of cardiac disease in hATTR-CM. However, recent studies have shown that strain imaging with echocardiography or MRI can detect changes within a 1-year time frame (Falk 2011; Benson et al. 2017). In addition, the cardiac biomarker N-terminal prohormone of brain natriuretic peptide (NT pro-BNP) has been shown to be elevated in patients with cardiac amyloidosis due to Primary Amyloidosis and to decline as cardiac function improves following

removal of the amyloid forming light chain protein with chemotherapy (Palladini et al. 2006). In the hATTR patient portion of this study, serum NT-proBNP will be assessed as an endpoint in all patients.

2.3 ION-682884

2.3.1 Mechanism of Action

ION-682884 is a second-generation antisense oligonucleotide (ASO) drug targeted to transthyretin, that has been covalently bonded to tri-antennary *N*-acetyl galactosamine (GalNAc), a high-affinity ligand for the hepatocyte-specific asialoglycoprotein receptor (ASGPR), to form an ASO-GalNAc conjugate. This GalNAc-conjugate approach results in enhanced ASO delivery to hepatocytes vs. non-parenchymal cells and has increased ASO potency at least 10-fold in mice(Prakash et al. 2014). The ASO portion of ION-682884 is complementary to a region within the 3′ untranslated region (3′ UTR) of the transthyretin mRNA and binds to the mRNA by Watson-Crick base pairing. The hybridization (binding) of ION-682884 to the cognate mRNA results in the RNase H1-mediated degradation of the transthyretin mRNA, thus preventing production of the transthyretin protein. Maximal antisense-mediated reduction of target mRNA levels is typically greater than 90% of control levels in sensitive tissues (Crooke et al. 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, ION-682884 is a synthetic oligomer of 20 nucleotides (i.e., a 20-mer) that are connected sequentially by phosphorothioate and phosphate diester internucleotide linkages, with a 5′-Trishexylamino-(THA)-C6GalNAc endcap. The nucleotide sequence of ION-682884 is complementary to a 20-nucleotide stretch within the 3′ UTR region of the transthyretin mRNA and is the same sequence shown to robustly impact disease progression in hATTR patients (refs). Structurally, the oligonucleotide has 4 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 ION-682884 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-catalyzed cleavage 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 enzyme (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. A fourth region is comprised of a tri-antennary cluster of *N*-acetyl galactosamine (GalNAc) sugars and is linked to the 5′ end of ION-682884 via a phosphodiester linkage. The GalNAc cluster is a high affinity ligand for the asialoglycoprotein

receptor (ASGPR), a receptor expressed primarily on the surface of liver hepatocytes (Stockert 1995). The GalNAc cluster enhances delivery of ION-682884 to liver hepatocytes over other cell types and enhances potency. After internalization into cells, the GalNAc cluster is metabolized to release 'free ASO' inside the cell (Prakash et al. 2014). The internucleosidic linkages are a mixture of phosphorothioate and phosphodiester. The phosphorothioate linkages are introduced into the DNA gap region and at both ends of the oligonucleotide to protect it from nuclease mediated metabolism. The mixed backbone design reduces the total number of phosphorothioate linkages which reduces non-specific interactions with proteins and further enhances potency and therapeutic index of GalNAc conjugated ASOs.

2.3.3 Preclinical Experience

Detailed information concerning the preclinical studies conducted with ION-682884 can be found in the Investigator's Brochure. A summary is included below.

The human TTR ASO, ISIS 420915, was identified from a broad screen of ASOs targeted to various regions of the human TTR pre-mRNA. ISIS 420915 was demonstrated to be potent and efficacious in reducing human TTR mRNA expression in the human HCC cell line HepG2. A 5′-GalNAc-conjugated mixed backbone variant of ISIS 420915, ION-682884, was synthesized and evaluated *in vitro* and *in vivo*. ION-682884 was found to be significantly more potent than the unconjugated parent ASO, ISIS 420915, in inhibiting TTR mRNA expression in human hepatocytes *in vitro* (approximately 51-fold improvement in potency, IC_{50}), with the potential to greatly increase the safety margins.

The activity of human TTR ASO ISIS 420915 has been characterized in both nonhuman primates and genetically-modified mice. While the sequence to which ISIS 420915 hybridizes is identical for human and cynomolgus monkeys, it is different in rodents. Therefore, human TTR transgenic mice were used as a model to test the pharmacologic effects of ISIS 420915. In human TTR transgenic mice, the ED_{50} values for human TTR hepatic mRNA and plasma protein reductions were 12.0 and 18.6 mg/kg/wk, respectively, following treatment with ISIS 420915 for 4 weeks. Treatment of cynomolgus monkeys with 50 mg/kg/wk ISIS 420915 for 12 weeks reduced TTR hepatic mRNA and plasma protein levels by approximately 80%.

ION-682884, which contains the GalNAc conjugate, significantly improved inhibition of human TTR hepatic mRNA and plasma protein levels in human TTR transgenic mice (with 28-fold and 15-fold increase in potency, ED_{50}, respectively), as compared to the unconjugated ASO, which is expected for this hepatocyte-expressed target. Treatment of cynomolgus monkeys for 13 weeks with 24 mg/kg/wk ION-682884 resulted in 60–70% reduction in TTR hepatic mRNA and plasma protein levels.

These results support the concept that inhibition of TTR through an antisense mechanism may serve as an effective strategy to ameliorate TTR-mediated amyloidosis. The results also strongly support GalNAc-conjugation to significantly increases ASO potency in inhibiting hepatic mRNA and plasma protein with lower doses providing the potential for improved safety.

2.3.4 Clinical Experience

ION-682884 has not been evaluated in any clinical setting. Please refer to the Investigator's Brochure for a detailed description of the preclinical pharmacology, nonclinical toxicology and

pharmacokinetics, as well as a description of previous clinical experience with other related 2′-MOE-phosphorothioate oligonucleotides.

ISIS 420915, also known as inotersen, an unconjugated 2′-*O*-(2-methoxyethyl) (2′-MOE) ASO that has the same base sequence as ION-682884, has been evaluated in clinical studies in more than 270 subjects and has shown an acceptable safety profile and clinical efficacy in patient populations in terms of clinical pharmacodynamics as well as measurements of primary efficacy endpoints mNIS+7 and Norfolk QoL-DN (Benson et al. 2018).

Significant treatment effect with inotersen on TTR levels was observed throughout the study in ISIS 420915-CS2 (Figure 1). In the inotersen group, mean percent changes from Baseline in circulating TTR levels decreased steadily through Week 13, which was the time frame when drug concentrations in the liver were expected to be approaching steady-state, and then were sustained for the (Yu et al. 2016a) duration of the Treatment Period. From Week 13 to Week 65, mean decreases in serum TTR ranged from 68.4% to 74.0% (median range: 74.6% to 79.0%) in the inotersen group. In the placebo group, mean serum TTR concentration decreased by 8.50% at Week 3 and then remained fairly constant throughout the Treatment Period.

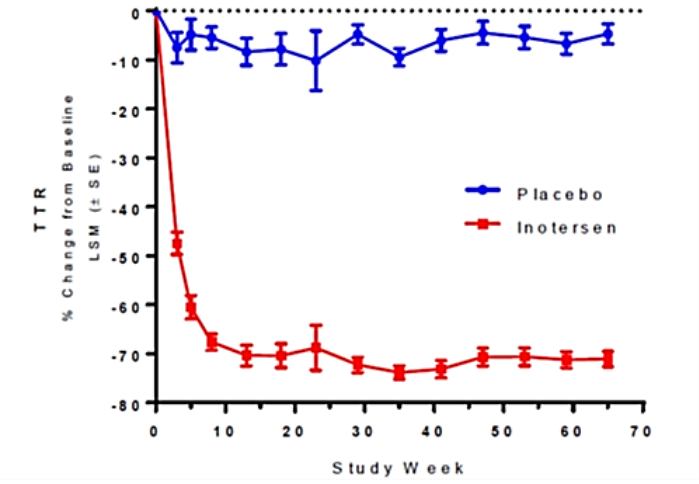


Figure 1 On-Treatment Percent Change from Baseline in TTR over Time

Changes from Baseline in mNIS+7 composite score showed a statistically significant difference in favor of inotersen compared with placebo at both Week 35 and Week 66. The difference in least squares means (LSMs) between treatment groups was -8.69 (95% confidence interval [CI]: -13.49, -3.90; p = 0.0005) and -19.73 (95% CI: -26.43, -13.03; p = 0.00000004) at Week 35 and Week 66, respectively (Figure 2). Changes from Baseline in Norfolk QoL-DN total score showed a statistically significant difference in favor of inotersen compared with placebo at both Week 35 and Week 66. The difference in LSMs between treatment groups was -6.14 (95% CI: -11.77, -0.52; p = 0.032) and -11.68 (95% CI: -18.29, -5.06; p < 0.0006) at Week 5 and Week 66, respectively (Figure 3).

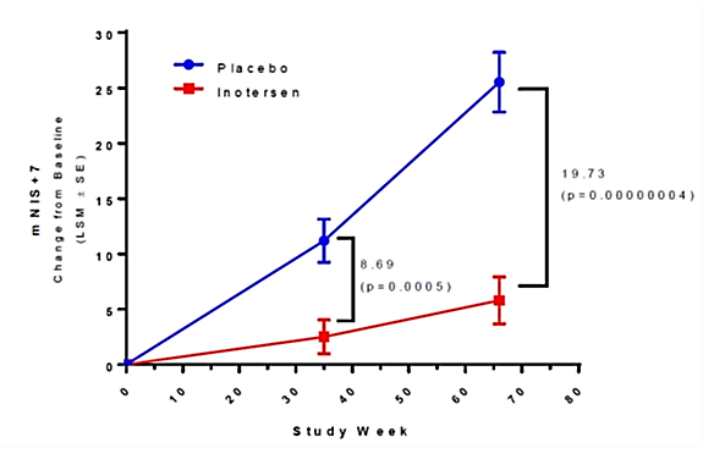


Figure 2 On-Treatment LSM Change from Baseline in mNIS+7 Composite Score

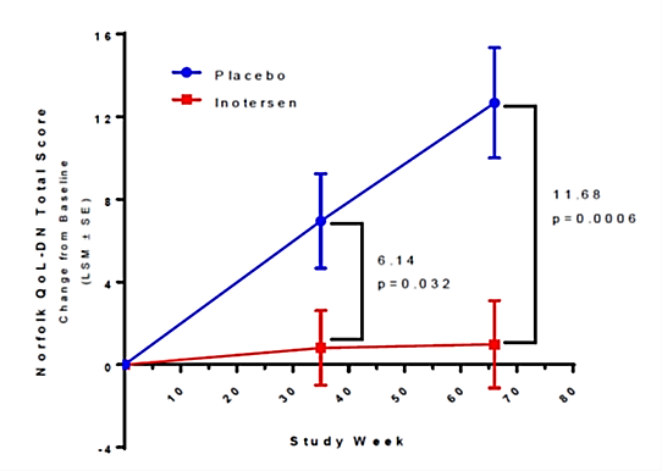


Figure 3 On-Treatment LSM Change from Baseline in Norfolk QoL-DN Total Score

Because the GalNAc conjugate approach results in enhanced ASO delivery to hepatocytes vs. nonparenchymal cells, thereby resulting in increased ASO potency, it is expected that significantly lower doses of ION-682884 will achieve similar target knockdown effects with an enhanced safety margin compared to inotersen.

2.4 Rationale for Dose and Schedule of Administration

Estimation of clinical doses for an antisense drug is less difficult than for most drugs in preclinical development. The numbers of variables that are normally encountered at this stage of development are reduced by the predictability of the pharmacokinetics of ASOs and the cumulative experience with other drugs in this class. The pharmacokinetics and disposition of many drugs in this class have been characterized and there are remarkable similarities from sequence to sequence and across species. In particular, the plasma pharmacokinetics for ASOs

in monkeys has been highly predictive of those in man. Because distribution to tissues is the dominant mechanism for plasma clearance, it can be assumed that plasma pharmacokinetic similarities translate into similarities in tissue distribution. This assumption is supported by the knowledge that patterns of tissue distribution for oligonucleotides are similar in mice, rats, rabbits, dogs and monkeys. Thus, it is possible to predict dose regimens on the basis of concentrations at the primary site of activity, the liver. Additionally, ASOs are hydrophilic and distribute predominantly to the lean body mass and in our experience, they should be administered as a fixed dose, rather than by total body weight.

Kidney and liver concentrations of ION-682884 collected after 13 weeks of dosing during a monkey toxicology study indicate that tissue distribution for this compound is consistent with previously administered antisense oligonucleotides. Post-distribution plasma concentrations (i.e., terminal elimination phase) of ION-682884 are expected to be in equilibrium with tissue concentrations in humans, as was observed in monkeys, mice, and rats for similar 2′-MOE gapmers with and without GalNAc-conjugation (Geary et al. 2003; Yu et al. 2016a; Yu et al. 2016b). The prolonged half-life of ION-682884 in liver of approximately 4 weeks observed in monkeys supports the monthly dosing regimens planned in the clinic. Moreover, this dosing schedule has been employed safely in previous clinical studies with a number of other phosphorothioate ASOs. Plasma pharmacokinetic analysis from this first clinical study will be used to characterize any differences from the nonclinical estimates and to adjust the estimates for subsequent clinical studies.

Safety data from the toxicology studies support a weekly or less frequent dose strategy. In the toxicology studies with ION-682884 in mice and monkeys, no clinical signs of overt toxicities were observed after 13 weeks of treatment (Study Nos. 682884-AS01 and -AS02, refer to the ION-682884 Investigator's Brochure).

The No Observable Adverse Effect Level (NOAEL) for ION-682884 was determined to be 6 mg/kg/wk (24 mg/kg/month). Pharmacokinetics observed in monkeys for ASOs predict the expected exposures in humans on the basis of mg/kg-equivalent doses (Geary et al. 2003; FDA Guidance for Industry 2005) (pgs 8-9); (Yu et al. 2007) and not on the basis of body surface area. This pharmacokinetic behavior is class-related and has been shown for all ASOs examined to date in the same chemical class as ION-682884. Therefore, the dose range of ION-682884 chosen for this initial study, 45 to 120 mg monthly (approximately 0.7 to 1.7 mg/kg body weight in a 70 kg subject), ranges from ~14- to 37-fold below the NOAEL and is considered a safe dose range for this trial.

In addition to the nonclinical experience of ION-682884, this dose range is supported by the nonclinical and clinical safety experience of more than 20 other 2′-MOE-modified ASOs including inotersen that have been safely administered intravenously and subcutaneously in multiple clinical studies at doses up to 1000 mg (Kwoh 2008) and for treatment durations that exceed 24 months.

2.5 Benefit-Risk Assessment

2.5.1 Healthy Volunteer Benefit Assessment

There are no potential benefits for healthy volunteers.

2.5.2 Patient Benefit Assessment

Administration of ION-682884 to patients may reduce the levels of mutated and wild-type TTR protein secreted by the liver, the primary source of TTR production and a primary organ for ASO distribution after systemic delivery. By decreasing the amount of liver-derived TTR protein circulating in the plasma, ION-682884 treatment may likely result in decreased formation of TTR amyloid fibril deposits and thus slows or halts disease progression.

2.5.3 Healthy Volunteer and Patient Risk Assessment

The known potential risks to study participants associated with ION-682884 are detailed in the Guidance to Investigator section of the Investigator's Brochure. Study associated potential safety considerations include thrombocytopenia, occurrence of glomerulonephritis, and retinol deficiency.

Thrombocytopenia and occurrence of glomerulonephritis are potential considerations based on clinical findings with inotersen, the unconjugated form of ION-682884, administered at a dose of 300 mg/wk. Frequent platelet, UPCR, and renal function monitoring as well as stopping rules will be implemented in this study.

In the event of confirmed platelet count declines ≤ 100,000/mm^3, more frequent monitoring will be implemented. The frequency of monitoring and additional laboratory tests will be determined by the Investigator in consultation with the Sponsor Medical Monitor or designee. In the event of a confirmed platelet count < 75,000/mm^3, Study Drug (ION-684882 or placebo) should be permanently discontinued and additional laboratory investigations will be conducted. Short-term steroid use will be recommended if platelet count drops to < 50,000/mm^3. This is based on data from other programs at Ionis demonstrating that short-term steroid use can improve recovery from thrombocytopenia. If the platelet result is unavailable (e.g., due to hemolysis, clumping, etc.) it must be repeated and reviewed prior to dosing during the Treatment Period.

Because TTR binds the retinol-RBP4 complex and prevents its excretion by the kidney, decreased plasma TTR levels result in decreased circulating levels of both RBP4 and retinol. This has been shown with the naturally occurring TTR Ile84 mutation that disrupts the TTR-RBP4-retinol complex and results in low plasma levels of retinol (Waits et al. 1995). Prolonged reduction of circulating retinol could result in impaired delivery of retinol to peripheral tissues and consequent signs and symptoms of vitamin A deficiency such as night blindness, xerophthalmia or retinopathy. However, chylomicrons are believed to provide an alternative route of delivery of retinyl esters to peripheral tissues (Wei et al. 1995) and chylomicron-delivered retinyl will not be affected by treatment with ION-682884. Indeed, preclinical studies utilizing TTR null mice have shown that although the mice have only 5–7% of circulating retinol and RBP4 levels compared to wild-type mice, they are viable and fertile, and do not show any observable symptoms of vitamin A deficiency (Episkopou et al. 1993; Wei et al. 1995). In addition, the levels of retinol within tissues such as the liver, kidney, testis and eye were similar in the TTR null mouse compared with wild-type controls (Wei et al. 1995). Furthermore, the retinal anatomy and function in these mice has been examined in detail with little effect found on the retinal structure or function (Bui et al. 2001). In addition, twins have been reported in the literature that have a genetic mutation in RBP4 that causes their RBP4 protein levels to be below the lower limit of quantification and also results in very low plasma retinol levels (Biesalski et al. 1999). In addition, mutations in the RBP4 gene have been

identified in 2 teenage siblings with no detectable serum RBP and retinol levels less than 20% normal (Biesalski et al. 1999; Seeliger et al. 1999). Despite the low retinol, they have normal retinyl esters levels, normal absorption of fat and vitamin A after a meal challenge, and they have mild night blindness and a modest retinal dystrophy but no pronounced effects on growth or other physiologic functions that are normally affected during vitamin A deficiency. Taken together these findings imply that RBP4 is not essential for maintaining adequate tissue retinol levels. To address the potential for impaired retinol delivery to tissues, in this study all patients will be required to take oral supplementation of the recommended daily allowance (RDA) of vitamin A (approximately 3000 IU vitamin A per day). In addition, an ophthalmic examination will be performed at Baseline and after approximately 13 weeks Post-Treatment. An electroretinogram (ERG) will also be performed at Baseline and at 13 weeks Post-Treatment to exclude subclinical tissue retinol deficiency.

2.5.4 Overall Assessment of Benefit:Risk

The measures taken to minimize risk to subjects participating in the healthy volunteer portion of this study, include a short duration of exposure, supplementation with vitamin A and frequent safety monitoring thus minimizing any potential risk. Additionally, in healthy volunteer studies, reductions in TTR have not been associated with any negative safety effects. The potential risks identified in association with ION-682884 in hATTR patients are justified by the anticipated benefits that may be afforded to those patients.

3. EXPERIMENTAL PLAN

3.1 Study Design

This will be a Phase 1/2, double-blind, randomized, placebo-controlled, dose-escalation study conducted at a single center for the healthy volunteer cohorts and will consist of 1 single-dose cohort and 2 multiple-dose cohorts (n = 12 per cohort, 10 active:2 placebo).

The open-label, hATTR patient cohort portion of the study will be conducted at multiple centers.

3.1.1 Healthy Volunteers (Cohorts A, B, C and E)

Multiple-Dose Cohorts

Cohort	Number of Doses	Total ION-682884
Cohort A: 45 mg ION-682884 or placebo SC	4	180 mg
Cohort B: 90 mg ION-682884 or placebo SC	4	360 mg

Subjects enrolled in the multiple-dose, healthy volunteer cohorts will receive SC doses of Study Drug once every 4 weeks for a total of 12 weeks (total of 4 doses). Following the administration of the 1st dose of Study Drug in each multiple-dose cohort, individual subjects must have completed their Day 15 safety evaluations with an acceptable safety profile, as determined by the Safety Committee (comprised of the Investigator, the Sponsor Medical Monitor and an Independent Safety Monitor), before receiving additional doses of Study Drug.

Dosing in Cohort B can only proceed when at least 8 subjects in Cohort A have completed Day 29 safety evaluations and have demonstrated an acceptable safety profile as determined by the Safety Committee.

Additional Multiple-Dose Cohort

The additional multiple-dose, healthy volunteer cohort (Cohort E) with 4 every-4-week doses of 60 mg ION-682884 or placebo, was added to further elucidate safety or PD effects of ION-682884.

Dosing in Cohort E can only proceed when at least 8 subjects in Cohort B have completed Day 29 safety evaluations and have demonstrated an acceptable safety profile as determined by the Safety Committee.

Cohort	Number of Doses	Total ION-682884
Cohort E: 60 mg ION-682884 or placebo SC	4	240 mg

For each dose cohort, the first 2 (sentinel) subjects (randomized 1 active:1 placebo) will be dosed on the same day. If no major safety concerns are observed following 48 hours of observation, as determined by the Safety Committee, dosing of the remaining 10 subjects (randomized 9 active:1 placebo) in that cohort may proceed.

Single-Dose Cohort

Cohort	Number of Doses	Total ION-682884
Cohort C: 120 mg ION-682884 or placebo SC	1	120 mg

Dosing in Cohort C can only proceed when at least 8 subjects in Cohort A have completed Day 57 safety evaluations and have demonstrated an acceptable safety profile as determined by the Safety Committee.

Subjects enrolled in the single-dose treatment cohort will receive a single SC dose of the Study Drug (ION-682884 or placebo) on Day 1. The first 2 (sentinel) subjects (randomized 1 active:1 placebo) will be dosed on the same day. If no major safety concerns are observed following 48 hours of observation, as determined by the Safety Committee, dosing of the remaining 10 subjects (randomized 9 active:1 placebo) in that cohort may proceed.

3.1.2 hATTR Patients (Cohort D)

This portion of the study will be multi-center and open-label and consists of 1 multiple-dose cohort with the dose level to be selected based upon on the results of the MAD cohorts in healthy volunteers.

Cohort	Number of Doses	Total ION-682884
Cohort D: ≤ 120 mg ION-682884	4	≤ 480 mg

Patients will receive SC doses of ION-682884 once every 4 weeks for a total of 12 weeks (total of 4 doses). Following the administration of the 1st dose of ION-682884, patients must have completed their Day 15 safety evaluations with an acceptable safety profile, as determined by the Safety Committee, before receiving additional doses of ION-682884.

3.2 Number of Study Centers

The healthy volunteer portion of the study will be conducted at a single center and the hATTR patient portion of the study will be conducted at multiple centers in Canada.

3.3 Number of Subjects

Approximately 36 healthy volunteers were planned to be enrolled in this study. Twenty-four (24), in the 2 planned multiple-dose cohorts and 12 subjects in the single-dose cohort. An additional multiple-dose cohort, Cohort E (n = 12), was added resulting in a total of approximately 48 healthy volunteers. If individual cohorts are expanded, a maximum enrollment of 60 subjects will be enrolled in the healthy volunteer, Phase 1 portion of the study.

Approximately 20 hATTR patients will be enrolled in the multi-dose, open-label, Phase 2 portion of the study. Additional patients may be added to better assess the safety, tolerability, pharmacokinetic and pharmacodynamic of ION-682884 to meet study objectives. Maximum enrollment will be limited to 30 hATTR patients.

The dosing cohorts are designed to assess the safety, tolerability, pharmacodynamics and pharmacokinetics of Study Drug (ION-682884 or placebo). The sample sizes are selected to ensure that the safety and tolerability of ION-682884 will be adequately assessed while minimizing unnecessary subject exposure.

3.4 Overall Study Duration and Follow-up

The study will consist of Screening, Treatment, and Post-Treatment Follow-up Periods. Please refer to the Schedule of Procedures in Appendix A.

Single-Dose Cohort (Cohort C)

The length of each subject's participation in Cohort C is approximately 17 weeks, including a 4-week Screening Period, a single-dose on Day 1 and 13 weeks of Post-Treatment Follow-up. Subjects will return for outpatient visits as outlined in Appendix A.

Multiple-Dose Cohorts (Cohorts A, B, D and E)

The length of each subject's participation in Cohorts A, B, D and E is approximately 29 weeks, including a 4-week Screening Period, a 12-week Treatment Period, and a 13-week Post-Treatment Evaluation Period. Subjects will receive a total of 4, once every 4 weeks, fixed SC doses of ION-682884.

At the end of the Treatment Period, eligible hATTR patients may elect to enroll in an open-label extension (OLE) study pending study approval by the IRB/IEC and the appropriate regulatory authority. Patients not participating in the OLE will enter the 13-week Post-Treatment Evaluation portion of this study unless consent is withdrawn.

Subjects may be required to attend additional visits for monitoring of adverse events or abnormal investigation results. The frequency of additional monitoring will be determined by the Study Medical Monitor in consultation with the Investigator.

3.4.1 Screening and Baseline Assessments

Healthy Volunteers (Cohorts A, B, C and E)

Subject eligibility for the healthy volunteer portion of the study will be determined within 4 weeks prior to study entry.

hATTR Patients (Cohort D)

For the hATTR patient portion of the study, a period of 6 weeks is given to complete the screening and baseline assessments outlined in the schedule of procedures. The baseline assessments should ideally be conducted after patient eligibility has been determined.

3.4.2 Treatment

Healthy Volunteers (Cohorts A, B, C and E)

Single-Dose

Eligible participants for Cohort C will report to the Study Center on Day -1 for study treatment on Day 1. There are 2 overnight stays in the clinic (Day -1 and Day 1). On Day 1, participants will receive a single SC dose of the Study Drug (ION-682884 or placebo). Please refer to the Schedule of Procedures in Appendix A for details on Study Day visits during the Treatment Period.

Multiple-Dose

Eligible participants in the multiple-dose Cohorts A, B and E will report to the Study Center on Day -1 for study treatment on Day 1. There are 3 overnight stays in the clinic (Day -1, Day 1, and Day 85). Participants will receive a SC dose of the Study Drug (ION-682884 or placebo) once every 4 weeks and will report to the Study Center for assessments at regular intervals throughout the Treatment Period. Please refer to the Schedule of Procedures in Appendix A for details on Study Day visits during the Treatment Period.

hATTR Patients (Cohort D)

Eligible participants in the multiple-dose Cohort D will report to the Study Center on Day -1 for study treatment on Day 1. There is 1 overnight stay in the clinic on Day -1. Participants will receive a SC dose of the ION-682884 once every 4 weeks and will report to the Study Center for assessments at regular intervals throughout the Treatment Period. Please refer to the Schedule of Procedures in Appendix A for details on Study Day visits during the Treatment Period.

3.4.3 Post-Treatment

Healthy Volunteers (Cohorts A, B, C and E)

Subjects will report to the Study Center for assessments at regular intervals throughout the Post-Treatment Period. Please refer to the Schedule of Procedures in Appendix A for details on Study Day visits.

hATTR Patients (Cohort D)

Patients will report to the Study Center for assessments at regular intervals throughout the Post-Treatment Period. Please refer to the Schedule of Procedures in Appendix A for details on Study Day visits. Alternatively, at the end of the Treatment Period, eligible patients may elect to enroll in an OLE study pending study approval by the IRB/IEC and the appropriate regulatory authority.

3.5 End-of-Study

The End-of-Study is defined as the date of the last visit of the last subject remaining in the study.

3.6 Safety Committee

A Safety Committee, comprised of the Investigator, the Sponsor Medical Monitor and an Independent Safety Monitor, will assess the safety and tolerability of the Study Drug (ION-682884 or placebo) throughout the study.

In addition, the Safety Committee will formally meet to determine whether:

- The safety and tolerability profile of the sentinel subjects in a cohort supports the dosing of the remaining subjects of that cohort
- The safety and tolerability profile of subjects after their Day 15 safety evaluations supports their receiving the remaining 3 doses of Study Drug
- The safety and tolerability profile of subjects in a cohort supports dose escalation to a higher-dose cohort

Safety Committee Meeting Schedule

Meeting #	Question for the Safety Committee	Data to be Reviewed	Allowed Action
1	Does the safety and tolerability profile of the sentinel subjects in Cohort A support the dosing of the remaining subjects in the cohort?	Observation of sentinel subjects for 48 hours post-dose to ensure no major safety or tolerability issues	Dosing of remaining 10 subjects in Cohort A
2	Have subjects in Cohort A completed their Day 15 safety evaluations with an acceptable safety profile and tolerability?	Day 15 safety and lab evaluations for subjects in Cohort A	Administration of remaining 3 doses of Study Drug to subjects in Cohort A
3	Have at least 8 subjects in Cohort A completed Day 29 safety evaluations and demonstrated an acceptable safety profile?	Day 29 safety and lab evaluations for at least 8 Cohort A subjects	Dosing of 2 sentinel subjects in Cohort B
4	Does the safety and tolerability profile of the sentinel subjects in Cohort B support the dosing of the remaining subjects in the cohort?	Observation of sentinel subjects for 48 hours post-dose to ensure no major safety or tolerability issues	Dosing of remaining 10 subjects in Cohort B
5	Have subjects in Cohort B completed their Day 15 safety evaluations with an acceptable safety profile and tolerability?	Day 15 safety and lab evaluations for subjects in Cohort B	Administration of remaining 3 doses of Study Drug to subjects in Cohort B
6	Have at least 8 subjects in Cohort A completed Day 57 safety evaluations and demonstrated an acceptable safety profile?	Day 57 safety and lab evaluations for at least 8 Cohort A subjects	Dosing of 2 sentinel subjects in Cohort C
7	Does the safety and tolerability profile of the sentinel subjects in Cohort C support the dosing of the remaining subjects in the cohort?	Observation of sentinel subjects for 48 hours post-dose to ensure no major safety or tolerability issues	Dosing of remaining 10 subjects in Cohort C
8	Have at least 8 subjects in Cohort B completed Day 29 safety evaluations and demonstrated an acceptable safety profile?	Day 29 safety and lab evaluations for at least 8 Cohort B subjects	Dosing of 2 sentinel subjects in additional Cohort E
9	Does the safety and tolerability profile of the sentinel subjects in Cohort E support the dosing of the remaining subjects in the cohort?	Observation of sentinel subjects for 48 hours post-dose to ensure no major safety or tolerability issues	Dosing of remaining 10 subjects in Cohort E
10	Have subjects in Cohort E completed their Day 15 safety evaluations with an acceptable safety profile and tolerability?	Day 15 safety and lab evaluations for subjects in Cohort E	Administration of remaining 3 doses of Study Drug to subjects in Cohort E
11	Have at least 8 subjects in Cohort B completed the Treatment Period (4 x 90 mg) and demonstrated an acceptable safety profile?	Safety and lab evaluations for at least 8 Cohort B subjects who completed the Treatment Period	Dosing of patients in Cohort D
12	Have patients in Cohort D completed their Day 15 safety evaluations with an acceptable safety profile and tolerability?	Day 15 safety and lab evaluations for patients in Cohort D	Administration of remaining 3 doses of ION-682884 to patients in Cohort D

3.7 Data and Safety Monitoring Board or Independent Data Monitoring Committee

An independent Data and Safety Monitoring Board (DSMB) will be assembled for Cohort D, the hATTR patient cohort of ION-682884-CS1. The DSMB will review the safety and tolerability of ION-682884 during Cohort D of the study at a frequency and duration as outlined in the Safety Management Plan and DSMB Charter.

3.8 Dose Escalation

Healthy Volunteers (Cohorts A, B, C and E)

Dosing of Cohort B (4 x 90 mg ION-682884 or placebo) can only proceed when at least 8 subjects in Cohort A (4 x 45 mg ION-682884 or placebo) have completed Day 29 safety evaluations and have demonstrated an acceptable safety profile as determined by the Safety Committee.

Dosing of Cohort C (1 x 120 mg ION-682884 or placebo) can only proceed when at least 8 subjects in Cohort A (4 x 45 mg ION-682884 or placebo) have completed Day 57 safety evaluations and have demonstrated an acceptable safety profile as determined by the Safety Committee

Dosing of the additional multiple-dose cohort, Cohort E, (4 x 60 mg ION-682884 or placebo) can only proceed when at least 8 subjects in Cohort B have completed Day 29 safety evaluations and have demonstrated an acceptable safety profile as determined by the Safety Committee.

hATTR Patients (Cohort D)

Enrollment in Cohort D (4 x ≤ 120 mg ION-682884) can only proceed when at least 8 subjects in Cohort B (4 x 90 mg ION-682884 or placebo) have completed the Treatment Period and have demonstrated an acceptable safety profile as determined by the Safety Committee.

The dose level for Cohort D will be informed by safety and PD data from the multiple-dose, healthy volunteer cohorts.

4. SUBJECT ENROLLMENT

4.1 Screening

Before subjects may be enrolled into the study, the Sponsor requires a copy of the Study Center's written institutional review board (IRB) approval of the protocol, informed consent form, and all other subject information and/or recruitment material.

Subjects or their legally acceptable representatives must sign the consent form before any screening tests or assessments are performed. At the time of consent, the subject 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 randomization or registration, subjects will be assigned a unique subject identification number. This number will be used to identify the subject throughout the trial and must be used on all study documentation related to that subject. The screening number and subject identification number must remain constant throughout the entire trial. Screening numbers and subject identification numbers, once assigned, will not be re-used.

4.2 Randomization/Registration

Subjects will be randomized (Cohorts A, B, C and E) or registered (Cohort D) after all Baseline and Screening assessments have been completed and after the Investigator has verified that they are eligible per criteria in Sections 5.1 and 5.2. No subject may begin treatment prior to randomization or registration and assignment of a unique subject identification number.

Within each single- and multiple-dose cohort, subjects will be randomized 10:2 to receive ION-682884 or placebo as outlined in Section 3.1. The Sponsor will prepare the randomization list.

4.3 Replacement of Subjects

Subjects withdrawn early from the study before completion of Day 8 assessments (Cohort C) or who do not complete all scheduled doses of Study Drug (ION-682884 or placebo) (Cohorts A, B and E) may be replaced at the discretion of the Sponsor unless the Safety Committee agree that this should not be done for reasons of safety. The additional subjects will be assigned to the same Study Drug (ION-682884 or placebo) as the subjects who are being replaced.

Subjects whose randomization code has been broken will not be replaced.

Hereditary transthyretin amyloidosis patients who withdraw from the study will not be replaced but will be encouraged to complete the 13-week, Post-Treatment Evaluation Period.

4.4 Unblinding of Treatment Assignment

For the healthy volunteer portion of the study, all subjects, monitors, and Study Center personnel related to the study, except for the pharmacist (or qualified designee) who dispenses/prepares the Study Drug (ION-682884 or placebo) and the pharmacy monitor (and pharmacy monitor report reviewer if applicable) who monitors the pharmacy records and procedures, will be blinded throughout the study. Sponsor personnel directly involved with the conduct of the study will also remain blinded throughout the study. However, if a subject has suffered a Serious Adverse Event (as defined in Section 9.3.3), and/or when knowledge of the treatment assignment will impact the clinical management of the subject, the Investigator will have the ability to unblind the treatment assignment for that subject. The Sponsor will be informed of the unblinding of a subject within 24 hours. An unblinded randomization schema will be maintained securely at the Study Center and the Sponsor's designated vendor. In addition, all SUSARs will be unblinded by the Sponsor for the purpose of regulatory reporting (see Section 9.2).

Every reasonable attempt should be made to complete the early termination study procedures and observations (see Appendices A and B) prior to unblinding, as knowledge of the treatment arm could influence subject assessment.

For each healthy volunteer cohort, an unblinded interim analysis of may be performed upon completion of dosing for that cohort to assess pharmacodynamic effect, and the results summarized by treatment group.

5. SUBJECT ELIGIBILITY

To be eligible to participate in this study candidates for the healthy volunteer portion of the study (Cohorts A, B, C and E) must meet the following eligibility criteria at within 28 days of Day 1 or at the time point specified in the individual eligibility criterion listed.

5.1 Inclusion Criteria for Healthy Volunteers (Cohorts A, B, C and E)

1. Must have given written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements
2. Healthy males or females of non-childbearing potential, aged 18 to 65 inclusive at the time of informed consent
3. Females must be non-pregnant and non-lactating, and either surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or post-menopausal (defined as 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved

   Males must be surgically sterile or abstinent*, if engaged in sexual relations with a female of child-bearing potential, the subject must be using an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 91 days (single-dose cohorts) or 13 weeks (multiple-dose cohorts) after the last dose of Study Drug (ION-682884 or placebo)

   * 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.
4. Willing to refrain from strenuous exercise/activity (for example heavy lifting, weight training, intense aerobics classes etc.) for at least 72 hours prior to study visits
5. Weight $\geq$ 50 kg and BMI $<$ 32 kg/m^2
6. Willingness to take vitamin A supplements

5.2 Exclusion Criteria for Healthy Volunteers (Cohorts A, B, C and E)

1. Clinically-significant abnormalities in medical history (e.g., previous acute coronary syndrome within 6 months of Screening, major surgery within 3 months of Screening) or physical examination
2. Screening laboratory results as follows, or any other clinically-significant abnormalities in screening laboratory values that would render a subject unsuitable for inclusion
   - Random spot urine protein/creatinine (P/C) ratio (UPCR) $\geq$ 200 mg/g. In the event of P/C ratio (UPCR) above this threshold ineligibility may be confirmed by a repeat random spot UPCR $\geq$ 200 mg/g or a 24-hr urine $\geq$ 200 mg/24 hr
   - Positive test (including trace) for blood on urinalysis. In the event of a positive test eligibility may be confirmed with urine microscopy showing $\leq$ 5 red blood cells per high power field

- ALT, AST, bilirubin, alkaline phosphatase, serum creatinine, BUN > ULN
- Fasting blood glucose > ULN
- Platelet count < LLN

3. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1
4. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator
5. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B
6. Uncontrolled hypertension (BP > 160/100 mm Hg)
7. 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.
8. Treatment with another investigational drug, biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever is longer
9. Previous treatment with an oligonucleotide (including siRNA) within 4 months of Screening if single dose received, or within 12 months of Screening if multiple doses received
10. History of bleeding diathesis or coagulopathy
11. Regular use of alcohol within 6 months prior to screening (> 7 drinks/wk for females, > 14 drinks/wk for males (1 drink = 5 ounces (150 mL) of wine or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of hard liquor), or use of soft drugs (such as marijuana) within 3 months prior to screening, or hard drugs (such as cocaine and phencyclidine) within 1 year prior to screening, or positive urine drug screen at Screening
12. Concomitant medication restrictions including OTC and herbal remedies, other than occasional acetaminophen (paracetamol) or ibuprofen unless authorized by the Sponsor Medical Monitor
13. Use of oral anticoagulants, unless the dose has been stable for 4 weeks prior to the first dose of Study Drug (ION-682884 or placebo) and regular clinical monitoring is performed
14. Smoking limitations: Smoking >10 cigarettes a day
15. Blood donation of 50 to 499 mL within 30 days of Screening or of > 499 mL within 60 days of Screening
16. Have any other conditions, which, in the opinion of the Investigator or Sponsor would make the subject unsuitable for inclusion, or could interfere with the subject participating in or completing the Study

5.3 Inclusion Criteria for hATTR Patients (Cohort D)

To be eligible to participate in this study cohort candidates must meet the following eligibility criteria within 6 weeks of Study Day 1, or at the time point specified in the individual eligibility criterion listed.

1. Must have given written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements
2. Aged 18 to 82 years at the time of informed consent.
3. Females must be non-pregnant and non-lactating, and either surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or post-menopausal (defined as 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved

   Males must be surgically sterile or abstinent*, if engaged in sexual relations with a female of child-bearing potential, the subject must be using an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 13 weeks after the last dose of ION-682884.

   * 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.
4. hATTR-PN as defined by:
   a. Polyneuropathy Disability (PND) Stage I-III
   b. Documented genetic mutation in the TTR gene
   c. Symptoms consistent with polyneuropathy as measured by NIS score > 5
   d. Willingness to take vitamin A supplements
5. BMI > 16 kg/m^2

5.4 Exclusion Criteria for hATTR Patients (Cohort D)

1. Clinically-significant abnormalities in medical history (e.g., previous acute coronary syndrome within 6 months of Screening, major surgery within 3 months of Screening) or physical examination
2. Screening laboratory results as follows, or any other clinically-significant abnormalities in screening laboratory values that would render a subject unsuitable for inclusion
   - ALT/AST > 1.9 x ULN
   - Bilirubin ≥ 1.5 x ULN (patients with bilirubin ≥ 1.5 x ULN may be allowed on study following discussion with the Study Medical Monitor if indirect bilirubin only is elevated, ALT/AST is not greater than the ULN and genetic testing confirming Gilbert's disease)
   - Platelets < 125 x 10^9/L

- Urine protein/creatinine (P/C) ratio (UPCR) ≥ 1000 mg/g. In the event of P/C ratio (UPCR) above this threshold ineligibility may be confirmed by a repeat random spot UPCR ≥ 1000 mg/g or a 24-hr urine ≥ 1000 mg/24 hr
- Renal insufficiency as defined by estimated creatinine clearance calculated according to the formula of CKD-EPI < 45 mL/min/1.73 m^2 at Screen. If the calculated creatinine clearance is thought to be artificially low, a 24-hr urine creatinine clearance can be completed with prior Sponsor approval
- TSH values outside normal range (unless approved by the Study Medical Monitor)

3. Serum retinol level at Screen < LLN

   For patients with a TTR mutation at position 84 (e.g., Ile84Ser or Ile84Asn) and retinol < LLN the exclusion criterion is signs or symptoms of vitamin A deficiency (such as dry eye, bitots' spot observed in the ophthalmology exam, that in the opinion of the ophthalmologist is consistent with vitamin A deficiency)
4. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1
5. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator
6. Known history of or positive test for HIV, hepatitis C or chronic hepatitis B
7. Uncontrolled hypertension (BP > 160/100 mm Hg)
8. 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. Patients with a history of other malignancies that have been treated with curative intent and which have no recurrence within 5 years may also be eligible if approved by the Sponsor Medical Monitor
9. Treatment with another investigational drug, biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever is longer. Does not apply to tafamidis, diflunisal, doxycycline or TUCA if subject has been on a stable dose of drug for ≥ 3 months and continues receiving the same dose for the duration of the study
10. Previous treatment with an oligonucleotide (including siRNA) within 3 months of Screening
11. Karnofsky performance status ≤ 50
12. Diagnosis of type 1 or type 2 diabetes for equal or more than 5 years; Screening HbA1c > 9.5%; or history of severe peripheral neuropathy due to diabetes
13. Other causes of sensorimotor or autonomic neuropathy (e.g., autoimmune disease)
14. Prior liver transplant or anticipated liver transplant within 1-yr of Screening
15. New York Heart Association (NYHA) functional classification of ≥ 3
16. NT-proBNP > 3000

17. Acute coronary syndrome or major surgery within 3 months of Screening
18. Known Primary Amyloidosis
19. Known Leptomeningeal Amyloidosis
20. Known Multiple Myeloma
21. Monoclonal gammopathy of undetermined significance (MGUS) unless serum M protein level of < 3 g/dL, < 10% clonal plasma cells in the bone marrow, urine monoclonal protein < 500 mg/24 hrs and no evidence of end-organ damage
22. Have any other conditions, which, in the opinion of the Investigator or Sponsor would make the subject unsuitable for inclusion, or could interfere with the subject participating in or completing the Study

6. STUDY PROCEDURES

6.1 Study Schedule

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

The safety of ION-682884 will be continually monitored throughout the trial by the Safety Committee. In addition, a Data and Safety Monitoring Board (DSMB) will be assembled for the hATTR patient cohort of this study to review safety, tolerability and efficacy (as needed) data collected on ION-682884. Based on its ongoing assessment of the safety and tolerability of ION-682884, the DSMB will provide recommendations to the Sponsor for modifying, stopping or continuing the hATTR patient cohort as planned.

6.1.1 Study Schedule for the Healthy Volunteers (Cohorts A, B, C and E)

The length of each subject's participation in Cohort C is up to approximately 17 weeks including a 4-week Screening Period and a 13-week Post-Treatment Evaluation Period.

The length of each subject's participation in Cohorts A, B and E is up to approximately 29 weeks, including a 4-week Screening Period, a 12-week (4-dose) Treatment Period, and a 13-week Post-Treatment Evaluation Period.

6.1.1.1 Screening Period

Written informed consent for the study will be obtained prior to the performance of any study-related procedures including screening procedures. A 28-day period is provided for completing screening assessments and determining subject eligibility for the study. Safety labs may be re-tested for determination of subject eligibility after consultation with the Sponsor Medical Monitor.

During the Screening Period, subjects will undergo a medical history and physical examination including vital signs, height and weight for BMI determination, and have blood and urine samples taken for clinical laboratory testing. Subjects will be screened for HIV, hepatitis B antigen, and hepatitis C antibody, as well as for drug and alcohol use.

Blood chemistry samples during screening should be taken after fasting for at least 8 hrs.

6.1.1.2 Treatment Period

Single-Dose

Subjects in Cohort C will be admitted to the Study Center on the evening prior to the single-dose administration (Day -1) and remain at the Study Center until discharge on Day 2 (2 overnight stays). Study Drug (ION-682884 or placebo) will be given on Day 1. The first 2 (sentinel) subjects (randomized 1 active:1 placebo) will be dosed on the same day. If no major safety concerns are observed following 48 hours of observation, as determined by the Safety Committee, dosing of the remaining 10 subjects (randomized 9 active:1 placebo) in that cohort may proceed.

Dosing of Cohort C (1 x 120 mg ION-682884 or placebo) can only proceed when at least 8 subjects in Cohort A have completed Day 57 safety evaluations and have demonstrated an acceptable safety profile as determined by the Safety Committee.

Multiple-Dose

The Treatment Period for all subjects in Cohorts A, B and E consists of 4 doses administered once every 4 weeks over the course of 13 weeks. Eligible subjects will be admitted to the Study Center on the evening prior to the first Study Drug administration (Day -1) and remain at the Study Center until discharge on Day 2 (2 overnight stays). Study Drug will be given on Day 1. For the last dose on Day 85, subjects will be admitted to the Study Center and remain until discharge on Day 86 (1 overnight stay).

Dosing of Cohort B (4 x 90 mg ION-682884 or placebo) can only proceed when at least 8 subjects in Cohort A (4 x 45 mg ION-682884 or placebo) have completed Day 29 safety evaluations and have demonstrated an acceptable safety profile as determined by the Safety Committee.

Dosing of the additional multiple-dose cohort, Cohort E, (4 x 60 mg ION-682884 or placebo) can only proceed when at least 8 subjects in Cohort B have completed Day 29 safety evaluations and have demonstrated an acceptable safety profile as determined by the Safety Committee.

6.1.1.3 Post-Treatment Period

Single-Dose

Subjects in Cohort C will be followed until Day 92. Subjects in Cohort C will return for outpatient visits on Days 3, 4, 8, 15, 29, 50, 71, and 92 for safety and clinical laboratory evaluations and for blood sampling for PK analysis.

Multiple-Dose

Subjects in Cohorts A, B and E will be followed until Day 176. During the Post-Treatment Evaluation Period, subjects will return to the Study Center for outpatient visits on Days 92, 99, 113, 127, 141, 155, and 176 for safety and clinical laboratory evaluations and for blood sampling for PK analysis.

6.1.2 Study Schedule for hATTR Patients (Cohort D)

The length of each subject's participation in Cohort D is up to approximately 29 weeks, including a 4-week Screening Period, a 12-week (4-dose) Treatment Period, and a 13-week Post-Treatment Evaluation Period.

6.1.2.1 Screening and Baseline

Before any study-specific procedures or evaluations are initiated, patients must sign and date the informed consent form. A 6-week period is given to perform the screening evaluations and baselines assessments which must be completed before Study Day 1. The TTR genotyping and amyloid biopsy tests may be conducted up to 10 weeks prior to Study Day 1. These tests are only conducted if appropriate documentation is not already available. The baseline assessments should ideally be performed after patient eligibility has been determined. An abnormal screening result may be retested for review by the Study Medical Monitor for eligibility purposes.

A NIS assessment is performed at Screening to determine patient eligibility only. This assessment does not include the +7 components.

The baseline assessment for mNIS+7 must be performed twice and the 2 assessments must be performed on separate days and within 14 days prior to the first dose of ION-682884 (Day 1). In addition, every effort should be made to conduct the 2 assessments < 7 days apart. If the ERG or ophthalmology examination are to be performed on a mNIS+7 assessment day, they must be performed **after** the mNIS+7 assessment is complete. The mNIS+7 assessment procedure includes the NIS, +7, and additional sensory and nerve conduction testing. The NSC score is collected during the NIS assessment procedure but is analyzed separately.

For a visit where the Norfolk QOL-DN questionnaire is to be administered, it must be the first assessment performed at the visit. Administration of the baseline Norfolk QOL-DN questionnaire should be done on the same day as the first mNIS+7 assessment, but **prior** to the mNIS+7 assessment.

For an individual patient, every effort should be made to ensure the same NIS evaluator performs all of the NIS assessments throughout the study. In addition, the NIS evaluator must be insulated from the patient's general study procedures and knowledge of the patient's adverse events.

6.1.2.2 Treatment Period

The Treatment Period for patients in Cohort D consists of 4 doses administered once every 4 weeks over the course of 13 weeks. Eligible subjects will be admitted to the Study Center on the evening prior to the first ION-682884 administration (1 overnight stay). ION-682884 will be given on Day 1.

Enrollment in Cohort D (4 x ≤ 120 mg ION-682884) can only proceed when at least 8 subjects in Cohort B (4 x 90 mg ION-682884 or placebo) have completed the Treatment Period and have demonstrated an acceptable safety profile as determined by the Safety Committee.

Dose level for Cohort D will be informed by PD data from Cohort A (4 x 45 mg doses), Cohort B (4 x 90 mg doses) and the additional healthy volunteer cohort, Cohort E, (4 x 60 mg

ION-682884) in conjunction with an acceptable safety profile in all cohorts as determined by the Safety Committee.

6.1.2.3 End-of-Treatment Efficacy Assessment Period

The end-of-treatment (EOT) efficacy assessments are conducted on Week 15.

The EOT efficacy assessments should also be performed on patients that terminate from treatment early. In this case, the early termination visit and EOT efficacy assessments should be performed at the same time.

6.1.2.4 Post-Treatment Period

Subjects in Cohort D will be followed until Day 176. During the Post-Treatment Evaluation Period, subjects will return to the Study Center for outpatient visits on Days 92, 99, 113, 127, 141, 155, and 176 for safety and clinical laboratory evaluations and for blood sampling for PK analysis.

6.2 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. Blood chemistry and urine samples (excluding 24-hr urine collection) should be taken after fasting for at least 8 hours. During this time the patient can drink water and they should ensure that they consume sufficient water in order to not become dehydrated.

If the platelet value, serum creatinine or liver enzyme tests are uninterpretable (e.g., due to clumping, hemolysis or quantity not sufficient) or missing, a repeat blood specimen should be re-drawn as soon as possible (ideally within 7 days).

6.2.2 Congestive Heart Failure

Any patient that develops signs, symptoms or test results suggestive of new onset or worsening (if pre-existing) congestive heart failure should have the following evaluations performed (in addition to any tests deemed to be necessary by the attending physician) as soon as possible and the Investigator should consider referral to a cardiologist:

- Chest x-ray
- 12 lead ECG
- Echocardiogram

6.2.3 Arrhythmias

Any patient that develops signs, symptoms or test results suggestive of new cardiac arrhythmia should have the following evaluations performed (in addition to any tests deemed to be necessary

by the attending physician) as soon as possible and the Investigator should consider referral to a cardiologist:

- 12 lead ECG
- Echocardiogram

6.2.4 Myocardial Ischemia

Any patient that develops signs, symptoms or test results suggestive of myocardial ischemia should have the following evaluations performed (in addition to any tests deemed to be necessary by the attending physician) and the Investigator should consider referral to a cardiologist:

- Serial 12 lead ECGs
- Serial cardiac enzyme evaluation (CKMB, cardiac troponin I or cardiac troponin T)

6.3 Restriction on the Lifestyle of Subjects

6.3.1 Contraception Requirements

Male subjects must refrain from sperm donation and either be abstinent† or, if engaged in sexual relations with a woman of child-bearing potential (WOCBP), the subject or the subject's non-pregnant female partner must use a highly effective contraception method from the time of signing the informed consent form until at least 13 weeks after their last dose of Study Drug. Highly effective contraception for the male subject comprises a vasectomy with negative semen analysis at Follow-up. Highly-effective contraception for WOCBP partners of male subjects comprises surgical sterilization (e.g., bilateral tubal occlusion), hormonal contraception associated with inhibition of ovulation (combined estrogen and progestogen containing, or progestogen-only), intrauterine contraception device or intrauterine hormone-releasing system (IUS). Male subjects with partners that are pregnant must use condoms to ensure that the fetus is not exposed to the Study Drug.

† Abstinence (i.e., refraining from heterosexual intercourse throughout the duration of study participation) 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.

Note: A female condom and a male condom should not be used together as friction between the 2 can result in either or both products failing.

6.3.2 Other Requirements

Subjects must refrain from taking strenuous exercise/activity (for example heavy lifting, weight training, intense aerobics classes etc.) for at least 72 hours prior to study visits.

All subjects will be required to fast for at least 8 hours before a blood sample is taken for the pharmacodynamic and retinol assessments.

7. STUDY DRUG

7.1 Study Drug Description

7.1.1 ION-682884

A solution of ION-682884 (150 mg/mL, 0.8 mL) contained in 2-mL stoppered glass vials and its storage and preparation instructions will be provided by the Sponsor. ION-682884 must be stored securely at 2–8 °Celsius and be protected from light.

7.1.2 Placebo

The placebo for this study is 0.9% sterile saline and will be provided by the Study Center.

7.2 Packaging and Labeling

The Sponsor will provide the Investigator with packaged ION-682884 labeled in accordance with specific country regulatory requirements. Placebo will be provided by the Study Center.

7.3 Study Drug Accountability

The study staff is required to document the receipt, dispensing, and return/destruction of ION-682884 supplies provided by the Sponsor according to Sponsor instruction and in accordance with institutional policy.

8. TREATMENT OF SUBJECTS

8.1 Study Drug Administration

ION-682884 solution and placebo will be prepared by an unblinded pharmacist (or qualified delegate) shortly before use, using aseptic technique. Vials are for single-use only. Study staff supporting the healthy volunteer portion of the study will be blinded to the identity of the drug. Doses of 45, 60, 90 and 120 mg will be administered as a single SC injection at the Study Center. Volumes to be administered are shown in Table 1. Please refer to the Study Drug Manual provided by the Sponsor for more detailed instructions for Study Drug (ION-682884 or placebo) preparation and administration.

Table 1 Study Drug Dosing Information

Cohort	Volume to Administer	Dose per Injection	Number of Doses	Total Dose
Cohort A	0.3 mL	45 mg ION-682884 or placebo	4	180 mg
Cohort B	0.6 mL	90 mg ION-682884 or placebo	4	360 mg
Cohort C	0.8 mL	120 mg ION-682884 or placebo	1	120 mg
Cohort D	≤ 0.8 mL	≤ 120 mg ION-682884	4	≤ 480 mg
Cohort E	0.4 mL	60 mg ION-682884 or placebo	4	240 mg

8.2 Other Protocol-Required Drugs

All study participants will take daily oral supplemental doses of the RDA of vitamin A (approximately 3000 IU vitamin A or the closest approximate dose as available in the region in which the patient resides). Commercially available vitamin A as a single supplement, or as part of a multivitamin, will be provided by the Study Center or designee, in accordance with local regulatory requirements and availability.

8.3 Other Protocol-Required Treatment Procedures

There are no other protocol-required treatment procedures.

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 the pre-dose tests closest to Day 1 and Day 1.

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 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 Study Drug (ION-682884 or placebo).

Re-dosing Guidance: Subjects with initial laboratory test values that reach a stopping rule must not be re-dosed until the re-test results are available. In general, subjects who do not meet the stopping rules based upon retest may continue dosing. However, the Safety Committee (or appropriately qualified designee) should confer as to whether additional close monitoring of the subject is appropriate. If any of the stopping criteria described below (refer to Sections 8.6.1 to 8.6.3) are met, the subject will be permanently discontinued from further treatment with Study Drug (ION-682884 or placebo), 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.

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: Subjects 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, ALP, 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 subjects 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 subject's ALT and/or AST levels reach 5 x ULN.

For a definition of Baseline, please refer to guidance in Section 8.5.

8.5.2 Safety Monitoring Rules for Platelet Count Results

Please refer also to Table 2.

Platelet count will be monitored at least every 2 weeks during the Treatment Period and for the first 4 weeks after discontinuation of treatment. The Investigator should review all platelet count results within 48 hours of receipt. If a patient's platelet count falls to 100,000/mm^3 or less, then the patient's platelet counts should be monitored weekly. In case of platelet reduction to below 75,000/mm^3, the platelet monitoring rule defined in Stopping rules (Section 8.6.3) should be followed.

Treatment should be held if there is no evaluable platelet count within the 2 weeks prior to the scheduled dose. Any unreportable platelet count result must be rechecked and determined not to have met a stopping rule before dosing can continue.

In the event of a platelet count < 75,000/mm^3, additional laboratory investigations should be conducted (Table 2).

Table 2 Additional Labs to be Performed in the Event of a Platelet Count < 75,000/mm^3

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 and mean platelet volume (MPV)
Serum B12 and folate
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 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

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

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, additional testing of coagulation parameters (aPTT, PT, INR) and platelet count should be performed.

8.6 Stopping Rules

For the purposes of the stopping rules, Baseline is defined as: the average of the pre-dose test closest to Day 1 and 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 subject with Study Drug (ION-682884 or placebo) will be stopped permanently; values that are not confirmed due 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, and/or concomitant eosinophilia (> ULN)

8.6.2 Stopping Rules for Renal Function Test Results

Healthy Volunteers (Cohorts A, B, C and E)

In the event of laboratory results for either of the following criteria, without an alternative explanation, dosing of a subject with Study Drug (ION-682884 or placebo) will be stopped permanently:

1. Confirmed serum creatinine increase that is both ≥ 0.3 mg/dL (26.5 µmol/L) and ≥ 40% above Baseline creatinine values (refer to definition of Baseline in Section 8.6)
2. Proteinuria: Random urine protein/creatinine (P/C) ratio ≥ 750 mg/g (confirmed by a repeat random spot UPCR ≥ 750 mg/g or a 24 hr UPCR ≥ 750 mg/24 hr

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

hATTR Patients (Cohort D)

In the event of a persistent elevation that is observed over 2 consecutive weeks, for either of the 2 criteria below, dosing of a patient with ION-682884 may be stopped temporarily:

1. A decrease in eGFR > 30%/min/1.73 mm^2
2. Proteinuria: Random urine protein/creatinine (P/C) ratio > 5x baseline AND > 150 mg/g; or absolute UPCR value > 2000 mg/g (confirmed by a repeat random spot UPCR ≥ 2000 mg/g or a 24 hr UPCR ≥ 2000 mg/24 hr)

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

8.6.3.1 Healthy Volunteers (Cohorts A, B, C and E)

In the event of a confirmed platelet count less than 75,000/mm^3, dosing of a subject with Study Drug (ION-682884 or placebo) will be stopped permanently. The platelet count should be tested weekly until it is above 75,000/mm^3 then subsequent monitoring should be per the schedule of procedures.

8.6.3.2 hATTR Patients (Cohort D)

Please refer also to Table 2.

In the event of any platelet count less than 25,000/mm^3, dosing of the patient with ION-682884 will be stopped permanently. Platelet count should be monitored daily until 2 successive values above 25,000/mm^3. Then monitor twice-weekly until 3 successive values above 75,000/mm^3. Then weekly monitoring until stable. Administration of steroids is recommended for patients whose platelet count is less than 25,000/mm^3. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2–4 weeks for 14 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:** Patient may require continuation with oral steroids after methylprednisolone).

In the event of a platelet count < 75,000/mm^3 and ≥ 25,000/mm^3, and in the absence of major bleeding or clinically-relevant non-major bleeding (defined below), dosing with ION-682884 should be suspended temporarily until the platelet count has recovered to > 100,000/mm^3. 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, and the speed of recovery of platelet count after interruption of dosing. If dosing is reinitiated, platelet count must be measured twice-weekly (consider more frequent monitoring if platelet count < 50,000/mm^3 and additional risk factors for bleeding are present [see Table 3]) until 3 successive values above 75,000/mm^3 then weekly until the end of study. Treatment should be held if there is no evaluable platelet count within the 2 weeks prior to the scheduled dose. 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 and Kearon 2005):

1. Fatal bleeding, and/or
2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarterial or pericardial, or intramuscular with compartment syndrome
3. Clinically-overt bleeding leading to transfusion of ≥ 2 units of packed red blood cells or whole blood or a fall in hemoglobin of 2.0 mg/dL (1.24 mmol/L) or more within 24 hours

Definition of Clinically-Relevant Non-Major Bleeding Events

Clinically-relevant non-major bleeding (CRNMB) is defined as overt bleeding not meeting the criteria for major bleeding but that resulted, for example, in medical examination, intervention, or had clinical consequences for a subject.

Definition of Minor Bleeding Events

Minor bleeding events are those that do not fulfill the criteria for major bleeding or clinically-relevant, non-major bleeding events (defined above), for example excess bruising, petechiae, gingival bleeding on brushing teeth.

Table 3 Actions in Patients with Low Platelet Count

If the subsequent test confirms the initial test result, then monitoring frequency and dosing should be adjusted as recommended in the table.

Platelet Count (/mm^3)	Monitoring Frequency	Dosing
≥ 100K	Every 2 weeks	Every 4-week dosing should be continued
≥ 75K to < 100K	Every week	Every 4-week dosing should be continued
≥ 50K to < 75K	Twice-weekly until 3 successive values above 75K then weekly monitoring.	Dosing should be paused until 3 successive values > 100K. On re-initiation of treatment, dosing frequency should be reduced from once every 4 weeks to once every 8 weeks
≥ 25K to < 50K‡*	Twice-weekly until 3 successive values above 75K then weekly monitoring. Consider more frequent monitoring if additional risk factors for bleeding are present.	Dosing should be paused until 3 successive values > 100K. On re-initiation of treatment, dosing frequency should be reduced from once every 4 weeks to once every 8 weeks Consider corticosteroids if additional risk factors for bleeding are present.
< 25K*	Daily until 2 successive values above 25K. Then monitor twice-weekly until 3 successive values above 75K. Then weekly monitoring until stable.	Treatment should be permanently discontinued. Corticosteroids strongly recommended.

‡ Additional risk factors for bleeding include age > 60 years, receiving anticoagulant or antiplatelet medicinal products, and /or prior history of major bleeding events

* In cases of severe thrombocytopenia, please consider based on PI clinical judgment, risk factors for TCP, and potential contraindication for corticosteroid, whether the patient would benefit from receiving glucocorticoid therapy to reverse the platelet decline as 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 24 weeks for 1-4 cycles; Prednisolone 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 and/or Treatment Schedule

Adjustment of dose and/or schedule is not permitted.

8.8 Discontinuation of Study Drug

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

- The subject becomes pregnant. Report the pregnancy according to instructions in Section 9.5.4
- The subject withdraws consent
- The subject experiences an adverse event that necessitates permanent discontinuation of study Drug
- The subject develops laboratory test abnormalities that meet any of the stopping rules listed in Sections 8.6.1 to 8.6.3
- The subject experiences an AE that necessitates unblinding of the Investigator to the subject's treatment assignment
- The subject meets any of the following Exclusion Criteria (see Section 5.4):
  - For Cohort D: if patient receives a liver transplant

The reason for discontinuation of Study Drug must be recorded in the electronic Case Report Form (eCRF) and source documentation.

Subjects who discontinue Study Drug will enter the Post-Treatment Period unless consent is withdrawn. For subjects withdrawn for reasons other than withdrawal of consent every effort should be made to complete the early termination of study procedures and observations at the time of withdrawal (see Appendix A) and ideally within 2 weeks from the last dose of Study Drug.

8.9 Withdrawal of Subjects from the Study Procedures

Subjects must be withdrawn from study procedures for any of the following:

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

Other reasons for withdrawal of subjects from study procedures 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 eCRF.

Any subject who withdraws consent to participate in the study will be removed from further treatment and study observation immediately upon the date of request. These subjects should be encouraged to complete the early termination study procedures and observations at the time of withdrawal (Appendix A).

For subjects withdrawn for reasons other than withdrawal of consent every effort should be made to complete the early termination of study procedures and observations at the time of withdrawal (see Appendix A) and ideally within 2 weeks from the last dose of Study Drug.

8.10 Cohort and Study Stopping Rules

Dosing of a cohort and the study, will be terminated, and no further dose escalation will occur, in the event that there is 1 SAE or 2 severe AEs in a cohort considered by the Safety Committee to be at least possibly-related to Study Drug. An exception to this rule, would be an SAE where the only seriousness criterion is hospitalization and the hospitalization was only for observation and no specific treatment was administered for the event leading to hospitalization.

8.11 Concomitant Therapy and Procedures

The use of concomitant therapies or procedures defined below must be recorded on the subject's eCRF. Adverse events related to administration of these therapies or procedures must also be documented on the appropriate eCRF.

8.11.1 Concomitant Therapy

Healthy Volunteers (Cohorts A, B, C and E)

A concomitant therapy is any non-protocol specified drug or substance (including over-the-counter medications, herbal medications and vitamin supplements) administered between signing of informed consent and the last study visit.

Allowed Concomitant Therapy

Acetaminophen (paracetamol) or ibuprofen may be used for symptomatic relief. Any other therapy should be approved by the Sponsor Medical Monitor or designee.

Disallowed Concomitant Therapy

The use of prescription and over-the-counter medications including nonsteroidal anti-inflammatory drugs and herbal remedies is prohibited during this study unless the occurrence of an AE requires a drug therapy. In such cases, the Investigator must consult the Sponsor Medical Monitor to decide on subject continuation or withdrawal from the study.

hATTR Patients (Cohort D)

Allowed Concomitant Therapy

Treatment with either Vyndaqel®, Diflunisal, doxycycline or TUCA is allowed only if the patient has been on a stable regimen for at least 4 weeks prior to screening and is planned to remain on a stable regimen through the end of the Post-Treatment Follow-Up period.

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

Disallowed Concomitant Therapy

All study participants are required to take daily RDA supplemental doses of vitamin A during the treatment and Post-Treatment evaluation periods. The vitamin A supplements will be provided by the Study Center or designee. A patient may choose to substitute the Study Center provided vitamin A supplement with their own, only after consultation with the Study Medical Monitor. Additional vitamin A supplements (other than those described above) are not allowed at any time during the study unless approved by the Study Medical Monitor (this includes multivitamin supplements that contain vitamin A).

The use of the following is allowed only if the patient has been on a stable regimen for at least 4 weeks prior to screening and is planned to remain on a stable regimen through the end of the Post-Treatment Follow-up Period:

- Due to known potential adverse effects of nonsteroidal anti-inflammatory drugs (NSAIDs), e.g., diflunisal, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers (ARBs) on renal function, it is recommended that they should be used with caution. Discussion with the Sponsor Medical Monitor prior to initiation of drugs that may affect renal function is recommended

8.11.2 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 26 visit.

8.12 Treatment Compliance

Compliance with treatment dosing is to be monitored and recorded in the eCRF by Study Center staff.

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 applicable Ionis and/or designee SOPs 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 GCP. 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.

In addition to the Investigator's assessment of relatedness, the Sponsor will evaluate the available information and perform an independent assessment of all reported SAEs and determine if there is a reasonable possibility that the Study Drug (ION-682884 or placebo) is causally related to a reported SAE. 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.

Appropriate personnel at the Sponsor will unblind SUSARs for the purpose of regulatory reporting. The Sponsor will submit SUSARs to Regulatory Agencies in blinded or unblinded fashion according to local law. The Sponsor will submit SUSARs to Investigators in a blinded fashion.

For Study Drug "expected" events, refer to the Investigator Brochure.

For the purpose of regulatory reporting of SUSARs, there are no "expected" AEs in this study population. For Study Drug (ION-682884 or placebo) "expected" AEs, refer to the Investigator's Brochure.

9.3 Definitions

9.3.1 Adverse Event

An adverse event (AE) can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not the AE is considered related to the medicinal (investigational) product.

An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)
- Recurrence of an intermittent medical condition (e.g., headache) not present at Baseline

- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from Study Drug

Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).

9.3.2 Adverse Drug Reaction and Unexpected Suspected Adverse Drug Reaction

Adverse Drug Reaction (ADR)

In the *pre-approval* clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not have been established, ADR is defined as follows:

> All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.

The phrase "responses to a medicinal product" means that a causal relationship between the medicinal product and the adverse event has been determined by the Sponsor as at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Suspected Unexpected Adverse Drug Reaction

A suspected unexpected ADR is any ADR, the nature or severity of which is not consistent with the applicable product information, e.g., Investigator's Brochure for an unapproved medicinal (investigational) product.

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 subject 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 a congenital anomaly or birth defect in the offspring of the subject (whether the subject 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 subject 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

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; OR Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials; the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

9.4 Monitoring and Recording Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a subject 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. Before a diagnosis is confirmed, all symptoms should be reported as separate AEs.

9.4.1 Serious Adverse Events

In the interest of subject safety, and in order to fulfill regulatory requirements**,** all SAEs (regardless of their relationship to Study Drug) should be reported to the Sponsor within 24 hours of the Study Center's first knowledge of the event. The collection of SAEs will begin after the subject signs the informed consent form and stop at the end of the subject's follow-up period which is defined as final study visit. When the Investigator is reporting by telephone, it is important to speak to someone in person vs. leaving a message. SAEs should be reported using an electronic SAE submission form whenever possible. In situations where the electronic SAE submission is unavailable, an Initial Serious Adverse Event Form should be completed, and a copy should be faxed or emailed to the Sponsor. The SAE reporting instruction, including the fax number and email address can be found in the investigator site file for the study.

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 subject's last protocol-specified follow-up visit will be evaluated by the Investigator and Sponsor. If the Investigator and Sponsor agree the subject'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 subject signs the informed consent form and will stop at the end of the subject's follow-up period, which is defined as the final study visit. The Investigator will monitor each subject 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 the Study Drug (ION-682884 or placebo) is characterized by one of the following:

- **Related:** There is clear evidence that the event is related to the use of Study Drug, e.g., confirmation by positive re-challenge test
- **Possible:** The event cannot be explained by the subject's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and Study Drug (ION-682884 or placebo) 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 Study Drug (ION-682884 or placebo) 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 subject's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and Study Drug

9.4.3.2 Severity

Healthy Volunteers

The severity of AEs and SAEs relating to laboratory tests and adverse events at the injection site will be graded based on criteria from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007 (refer to Appendix D). Any AE not listed in Appendix D will be graded as follows:

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

hATTR Patients

The severity of AEs and SAEs relating to laboratory tests and adverse events at the injection site will be graded based on criteria from the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, November 2017 (refer to Appendix D). Any AE not listed in Appendix D will be graded as follows:

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

Action taken with Study Drug (ION-682884 or placebo) due to the event is characterized by one of the following:

- **None:** No changes were made to Study Drug (ION-682884 or placebo) administration and dose
- **Not Applicable:** SAE/AE was reported during Screening Period prior to Study Drug administration
- **Permanently Discontinued:** Study Drug was discontinued and not restarted
- **Temporarily Interrupted, Re-started – Same Dose:** Dosing and/or dosing frequency was temporarily interrupted/changed or delayed due to the AE and restarted at the same dose
- **Reduced Dose:** Dosing was reduced, temporarily interrupted or delayed due to the AE and restarted at the next lower dose or reduced dosing frequency

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 eCRF, 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 an 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)
- **Recovered with Sequelae:** The signs/symptoms of the reported SAE have improved but not completely resolved, and a new baseline for the subject is established since full recovery is not expected
- **Fatal:** Patient died (the date of death should be entered as the SAE resolution date)
- **Unknown:** The outcome of the reported SAE is not available, e.g., patient is lost to follow-up

9.4.3.6 Follow-up of Adverse Event

Investigator Follow-Up

During the study period, the Investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to Study Drug or related to study procedures until a final outcome can be reported.

Resolution of AE (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

Investigator should follow-up or support the Sponsor's effort to follow up with all pregnancies reported during the study from either the study subject or the female partner of male study subject until pregnancy outcome is available.

Sponsor Follow-Up

For SAEs, AESI and pregnancy cases in subjects who has completed or terminated study, the Sponsor or a designee should follow-up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

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 Safety Committee. 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 subject 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 subject'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 subject'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

Study Drug (ION-682884 or placebo) errors (including overdose, underdose, and administration error) should be documented as Protocol Deviations. A brief description should be provided in the deviation, including whether the subject 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 subject takes a dose of Study Drug (ION-682884 or placebo) that exceeds protocol specifications and the subject is symptomatic, then the symptom(s) should be documented as an AE and be reported per Section 9.4.

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or

incorrect administration of Study Drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

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 within 24 hours.

9.5.4 Contraception and Pregnancy

Subjects must continue to use appropriate contraception with their partners, or refrain from sexual activity, as described in Section 6.3.1.

If a subject becomes pregnant or a pregnancy is suspected, or if a male subject 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 **within 24 hours** of first learning of the occurrence of pregnancy. Follow-up information including delivery or termination is reported by designating as 'Follow-up' on the Pregnancy Forms and reported within 24 hours.

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

Female subjects: If a suspected pregnancy occurs while on the study (including follow-up), a pregnancy test will be performed. The subject with a confirmed pregnancy will be immediately withdrawn from treatment with Study Drug. However, the subject 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 subject 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 to obtain additional information relevant to the pregnancy progress and outcome**.** A longer follow-up may be required if a newborn child experiences a medical condition. Follow-up will be performed to the extent permitted by the applicable regulations and privacy considerations; e.g., pregnancy ICF may be required.

Male subjects: The progress of the pregnancy of a male subject'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 follow-up with the mother and may request access to the mother and infant's medical records** to obtain additional information relevant to the pregnancy progress and outcome. A longer follow-up may be required if a newborn child experiences a medical condition. Follow-up will be performed to the extent permitted by the applicable regulations and privacy considerations; e.g., partner ICF may be required.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Subsets, and Covariates

Analysis of safety labs, AEs, concomitant medications, ECG and physical examinations of healthy volunteers and patients with TTR amyloidosis following subcutaneously administration of single and/or multiple doses of ION-682884.

10.1.2 Secondary Endpoints

10.1.2.1 Pharmacokinetic Endpoints

The plasma pharmacokinetics of ION-682884 (as total full-length oligonucleotide, including fully conjugated, partially conjugated, and unconjugated ION-682884) will be assessed following single and multiple SC administration. The amount of ION-682884 excreted in urine over selected 24-hour collection intervals will be determined. Metabolite identification and profiling may be determined in some of the collected plasma, urine, and fecal samples at a later time.

10.1.2.2 Pharmacodynamic Endpoints

Analysis of pharmacodynamic data will determine the change and percent change from Baseline in plasma TTR and RBP4 levels following single- and multiple-dose SC administration of Study Drug.

10.1.3 Additional/Exploratory Endpoints

Exploratory endpoints for the open-label, hATTR patient cohort are the change from Baseline to Week 15 in the:

- mNIS +7 score
- Norfolk QOL-DN questionnaire total score
- 6MWT
- 10MWT
- EQ-5d
- SF-36 questionnaire domain scores
- COMPASS-31 questionnaire
- Amyloidosis-specific QoL questionnaire

10.2 Sample Size Considerations

There is no statistical rationale for the selected sample size of the single-dose and multiple-dose treatment cohorts. The sample size was based on prior experience with second generation ASOs in healthy volunteers to ensure that the safety, tolerability, PK, and preliminary PD of ION-682884 will be adequately assessed while minimizing the unnecessary subject exposure.

10.3 Populations

Full Analysis Set: All randomized subjects who received at least 1 injection of Study Drug (ION-682844 or placebo).

Per Protocol Set: Subset of the Full Analysis Set that have received at least a certain percentage of the prescribed doses of Study Drug and that have no significant protocol deviations that would be expected to affect efficacy assessments.

Safety Set: All randomized subjects who receive at least 1 injection of Study Drug.

Pharmacokinetic Set: All subjects who are randomized and receive at least 1 dose of active Study Drug (ION-682844) and have at least 1 evaluable PK sample.

10.4 Definition of Baseline

Baseline will be defined as the average of the pre-dose measurement closest to Day 1 and Day 1 Pre-dose. Day 1 Pre-dose is the Day 1 measurement taken prior to the time of the first dose.

For other assessments, baseline will be defined as the last non-missing measurement prior to the date and time of the first dose of Study Drug (ION-682884 or placebo).

The 2 mNIS+7 assessments must be performed on separate days and within 14 days prior to the first dose of Study Drug (Day 1). In addition, every effort should be made to conduct the 2 assessments < 7 days apart.

10.5 Interim Analysis

Unblinded analyses will be conducted after completion of dosing in each healthy volunteer cohort.

10.6 Planned Methods of Analysis

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. Where appropriate, p-values will be reported. All statistical tests will be conducted using 2-sided tests with 5% Type I error rate unless otherwise stated.

The placebo subjects will be pooled and analyzed for multiple-dose placebo groups in Cohort A, B and E.

10.6.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics by treatment group. Patient randomization will be summarized by cohort and treatment group. The subject disposition will be summarized. All subjects enrolled will be included in a summary of subject disposition.

10.6.2 Safety Analysis

The safety analysis will be conducted on the Safety Set.

Treatment duration and amount of Study Drug (ION-682884 or placebo) received will be summarized by treatment group. Subject incidence rates of all adverse events will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class, and by MedDRA term.

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 (ION-682884 or placebo) will be summarized.

Laboratory tests to ensure subject safety including chemistry panel, complete blood count with differential, coagulation panel, complement etc., will be summarized by study visits for each treatment group. These safety variables will also be presented as change and percent change from Baseline over time after Study Drug (ION-682884 or placebo) administration, as appropriate.

Vital sign and ECG measures will be tabulated by treatment group. In addition, the number of patients who experience abnormalities in clinical laboratory evaluations will be summarized by treatment group.

10.6.3 Pharmacokinetic Analysis

The plasma PK of ION-682884 (as total full-length ASO) will be assessed following single and multiple SC administration. The amount of ION-682884 (as total full-length ASO) excreted in urine over 24-hr intervals will be determined following single and multiple doses. Metabolite identification and profiling may be determined in some of the collected plasma, urine, and fecal samples at a later time.

Noncompartmental PK analysis of ION-682884 will be carried out on each individual subject data set. The C_{max} and the T_{max} will be obtained directly from the concentration-time data. The plasma half-life ($t_{1/2\ \lambda z}$) associated with the apparent terminal elimination phase will be calculated, if appropriate using available data, from the equation, $t_{1/2\lambda z} = 0.693/\lambda_z$, where λ_z is the rate constant associated with the apparent terminal elimination phase. Partial areas under the plasma concentration-time curve from zero time (pre-dose) to selected times (t) after the SC administration ($AUC_{0\text{-}t}$) will be calculated.

The amount of ION-682884 excreted in the urine will be determined from the following expression:

$$AAAA_{tt} = CC_{uuuuuuuuAA} \; xx \; VV_{uuuuuuuuAA}$$

Where, Ae_t is the amount excreted up to some fixed time (t) (i.e., 24 hours), C_{urine} is the urine concentration of the analyte, and V_{urine} is the total urine volume. The percentage of the administered dose excreted in urine will then calculated from the following expression:

$$\%\ DDDDDDAA\ EExxEEuuAAttAAEE = \left(\frac{AAAA_{tt}}{\frac{AAEEAAuuuuuuuDDttAAuuAAEE}{DDDDDDAA}} \right) xx\ 100\%$$

Other plasma and urine PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist.

Plasma and urine PK parameters will be summarized using descriptive statistics. Additional details regarding the PK analysis will be described in the Statistical Analysis Plan.

Potential relationships between selected PD (e.g., TTR level), safety (e.g., ECG parameters) and PK measures may also be explored, where deemed appropriate.

10.6.4 Pharmacodynamic Analysis

The PD analysis will be conducted in the Full Analysis Set and Per Protocol Set. The change and percent change from baseline in TTR and RBP4 will be summarized.

10.6.5 Additional Analyses

Exploratory endpoints for the hATTR patient cohort will be summarized. Details will be described in the SAP.

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 subject's participation in the trial, the Investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any Study Drug (ION-682884 or placebo) are administered. The subject must be given sufficient time to consider whether to participate in the study.

The acquisition of informed consent and the subject's agreement or refusal to notify his/her primary care physician should be documented in the subject's medical records and the informed consent form should be signed and personally dated by the subject 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 subject.

11.2 Ethical Conduct of the Study

All 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 must be followed.

11.3 Institutional Review Board

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the 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 subjects into the study and shipment of Study Drug. A copy of the written approval of any other items/materials that must be approved by the Study Center or IRB must

also be received by the Sponsor before recruitment of subjects into the study and shipment of Study Drug. The Investigator's Brochure must be submitted to the IRB for acknowledgement.

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

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

11.4 Subject Confidentiality

The Investigator must ensure that the subject's confidentiality is maintained. On the case report forms or other documents submitted to the Sponsor, subjects should be identified by initials (if permitted by local law) and a subject identification 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 IRB direct access to review the subject'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 subject to permit named representatives to have access to his/her study-related records without violating the confidentiality of the subject.

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 IRB must be informed of all amendments and give approval for any amendments likely to affect the safety of the subjects or the conduct of the trial. The Investigator **must** send a copy of the approval letter from the IRB to the Sponsor.

12.2 Study Termination

The Sponsor reserves the right to terminate the study. The Investigator reserves the right to terminate their participation in the study, according to the terms of the site contract. The Investigator should notify the 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 subject's case report form 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, eCRF may not be used as source documents.

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

- Subject files containing completed case report forms, 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 IRB and the Sponsor
- If drug supplies are maintained at the Study Center, proof of receipt, Study Drug Product Accountability Record, Return of Study Drug Product for Destruction, final Study Drug product reconciliation, and all drug-related correspondence

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

No study document should be destroyed without prior written agreement between the Sponsor 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., case report forms and other pertinent data) provided that subject confidentiality is respected.

The Sponsor monitor is responsible for inspecting the case report forms 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 subject medical records and other study-related records needed to verify the entries on the case report forms.

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 case report forms, 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 subject data received by the Sponsor. During this review, subject 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 case report form. These signatures will indicate that the Principal Investigator inspected or reviewed the data on the case report form, 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 and trade names are acceptable for concomitant medications. Combination medications should be recorded using their trade name.

All written information and other material to be used by subjects 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. Subjects 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

Single-Dose Cohort C

Multiple-Dose Cohorts A, B and E

Multiple-Dose Cohort D

Appendix A Schedule of Procedures - Single-Dose Cohort C

	Screen	Pre-Treatment	Single-Dose and Post-Treatment Evaluation									
Study Day	-28 to -2	-1	1	2	3	4	8 or Early Term	15	29	50	71	92
Visit Window	0	0	0	0	0	1	1	2	2	2	2	2
Overnight Stay		X	X									
Informed Consent	X											
Inclusion/Exclusion	X	X										
Medical History	X											
Body Weight and BMI	X											
Physical Exam[1]	X	X					X		X			X
Vital Signs[2]	X	X	X•	Xb	X	X	X	X	X	X	X	X
HIV, Hepatitis B & C	X											
FSH[3]	X											
Pregnancy Test[4]	X	X					X		X			X
Chemistry Panel (Fasting)[5, 6]	X		X•	Xb		X	X	X	X	X	X	X
Hematology[6]	X		X•	Xb		X	X	X	X	X	X	X
Urinalysis	X		X•	Xb		X	X	X	X	X	X	X
PD Panel[5]	X		X•	Xb		X	X	X	X	X	X	X
Inflammatory Panel			X•		XC		X					X
Complement (C5a, Bb)			Xd	Xb			X					
PT, **INR**, aPTT	X		Xd	Xb			X					
ECG (12-Lead, triplicate)	X		X•	Xb			X		X			X
Thyroid Panel	X											
Drug/Alcohol Screen[7]	X	X										
Study Drug Administration			X									
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X

Appendix A Schedule of Procedures – Single-Dose Cohort C *Continued*

	Screen	Pre-Treatment	Single-Dose and Post-Treatment Evaluation									
Study Day	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**8 or Early Term**	**15**	**29**	**50**	**71**	**92**
Visit Window	**0**	**0**	**0**	**0**	**0**	**1**	**1**	**2**	**2**	**2**	**2**	**2**
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
PK Blood Sampling[8]			X[f]	X[b]			X	X	X	X	X	X
PK 24-hr Urine Sampling[8, 9]			X									
PK 24-hr Fecal Collection[8, 9]			X									
Immunogenicity Testing[10]			X[a]					X	X			X
Archived Serum/Plasma Samples[11]			X[a]	X[b]	X	X	X	X	X	X	X	X

Note: If not specifically labeled, "X" means anytime

Subjects that terminate early during the Post-Treatment Period should complete all procedures for Study Day 8

1 Full physical exam to be given at Screening and abbreviated physical exam to be given thereafter

2 Blood Pressure (BP), Heart Rate (HR), Respiration Rate (RR), temperature

3 Women who are not surgically sterile as confirmation of menopause

4 Women who are not surgically sterile as confirmation of menopause. Dipstick acceptable at Day-1 only. Serum test at all other timepoints

5 Fasted samples should be taken after fasting for at least 8 hours and preferably not more than 12 hours. During this time the patient can drink water and they should ensure that they consume sufficient water in order to not become dehydrated

6 If the platelet value, serum creatinine or liver enzyme tests are uninterpretable (e.g., due to clumping, hemolysis or quantity not sufficient) or missing a repeat blood specimen should be re-drawn as soon as possible (ideally within 7 days)

7 Urine-test at Screening will be sent to the Central Laboratory for analysis. Day -1 will be done at the site using e.g., a breathalyzer or a urine test

8 Refer to Appendix C for PK sampling schedule

9 Start 24-hr urine and fecal PK collection post SC injection of ION-682884. Pool and record total urine volume. Ensure subjects have voided bladder prior to start of dosing

10 If time is not specified, Immunogenicity testing can be done at any time

11 Stored at -70 °C for follow-up exploration of pharmacodynamics, laboratory findings and/or adverse events (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, etc.) in this or subsequent clinical studies of ION-682884

Time (time is in reference to Study Drug administration):

a Pre-dose
b 24 hours
c 48 hours
d Pre-dose, 3 hours
e Pre-dose, 1, 2, 3, 4, 8 hours
f Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 hours

Appendix A Schedule of Procedures - Multiple-Dose Cohorts A, B and E

	Screen	Pre-Treatment	Treatment Period[1] (13 Weeks)												Post-Treatment Evaluation Period[1] (13 Weeks)						
Study Week	-4 to -1	-1	1			2	3	5	7	9	11	13			14	15 or ET	17	19	21	23	26 or ET FU
Study Day	-28 to -2	-1	1	2	3	8	15	29	43	57	71	85	86	87	92	99	113	127	141	155	176
Visit Window (days) (+/-)	0	0	0	0	0	2	2	2	2	2	2	1	1	1	2	2	2	2	2	2	2
Overnight Stay		X	X									X									
Informed Consent	X																				
Inclusion/Exclusion	X	X																			
Medical History	X																				
Body Weight and BMI	X															X					X
Physical Exam[2]	X	X													X	X					X
Vital Signs[3]	X	X	X•	Xb	XC	X	X	X•	X	X•	X	X•	Xb	XC	X	X	X	X	X	X	X
HIV, Hepatitis B & C	X																				
FSH[4]	X																				
Pregnancy Test5	X	X							X						X	X			X		X
Chemistry Panel[7] (Fasting[6])	X		X•	Xb		X	X	X•	X	X•	X	X•	Xb		X	X	X	X	X	X	X
Hematology[7]	X		X•	Xb		X	X	X•	X	X•	X	X•	Xb		X	X	X	X	X	X	X
Urinalysis	X		X•	Xb		X	X	X•	X	X•	X	X•	Xb		X	X	X	X	X	X	X
PD Panel (Fasting[6])	X		X•			X	X	X•	X	X•	X	X•			X	X	X	X	X		X
Inflammatory Panel			X•	Xb	XC		X	X•				X•	Xb	XC	X	X					X

Appendix A Schedule of Procedures -Multiple-Dose Cohorts A, B and E *Continued*

	Screen	Pre-Treatment	Treatment Period[1] (13 Weeks)												Post-Treatment Evaluation Period[1] (13 Weeks)						
Study Week	-4 to -1	-1	1			2	3	5	7	9	11	13			14	15 or ET	17	19	21	23	26 or ET-FU
Study Day	-28 to 2	-1	1	2	3	8	15	29	43	57	71	85	86	87	92	99	113	127	141	155	176
Visit Window (days) (+/-)	0	0	0	0	0	2	2	2	2	2	2	1	1	1	2	2	2	2	2	2	2
Complement (C5a, Bb)			Xd	Xb				X•				X•			X	X					X
PT, INR, aPTT	X		Xd	Xb				X•				X•			X	X					X
ECG (12-Lead)	X		Xe	Xb								Xe	Xb		X	X					X
Thyroid Panel	X																				
Drug/Alcohol Screen[8]	X	X																			
Study Drug Administration			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
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK Blood Sampling[9]			X!	Xb	XC	X	X	X•	X	X•	X	Xt	Xb	XC	X	X	X	X	X	X	X
PK 24-Hr Urine Sampling[9,10]			X									X									
PK 24-hr Fecal Collection[9, 10, 11]			X									X									
Immunogenicity Testing[12]			X•				X	X•							X	X					X
Archived Serum/Plasma Samples[13]			X•	Xb	XC	X	X	X•	X	X•	X	X•	Xb	XC	X	X	X		X		X

Note: If not specifically labeled, "X" means any time

A 10-minute time window applies to all procedures to allow for flexibility where multiple procedures are scheduled at the same time

Appendix A Schedule of Procedures –Multiple-Dose Cohorts A, B and E *Continued*

Legend *Continued*

1 Subjects who terminate early from the Treatment Period of the study should be encouraged to participate in the Post-Treatment Period. If the subject agrees, the subject should complete the Early Termination (ET) visit approximately 2 weeks after the last dose of Study Drug, followed by subsequent Post-Treatment visits. Subjects who terminate early from the Post-Treatment Period (and subjects who terminate early from the Treatment Period of the study and do not agree to participate in the Post-Treatment Period) should be encouraged to complete an ET visit

2 Full physical exam to be given at Screening and abbreviated physical exam to be given during Treatment and Post-Treatment Period as indicated to assess changes from Screening

3 Blood Pressure (BP), heart rate (HR), respiratory rate (RR), temp

4 Women who are not surgically sterile as confirmation of menopause

5 Conducted only in women who are not surgically sterile. Dipstick acceptable at Day -1 only; all other pregnancy tests should be conducted on serum or plasma samples

6 Fasted samples should be taken after fasting for at least 8 hours and preferably not more than 12 hours. During this time the patient can drink water and they should ensure that they consume sufficient water in order to not become dehydrated

7 If the platelet value, serum creatinine or liver enzyme tests are uninterpretable (e.g., due to clumping, hemolysis or quantity not sufficient) or missing a repeat blood specimen should be re-drawn as soon as possible (ideally within 7 days)

8 Urine-test at Screening will be sent to the Central Laboratory for analysis. Day -1 will be done at the site using e.g., a breathalyzer or a urine test

9 See Appendix C for specific PK schedules

10 Start 24-hr urine and fecal PK collection post SC injection of ION-682884. Pool and record total urine volume. Ensure subjects have voided bladder prior to start of dosing

11 Fecal PK only to be collected for Cohort B

12 If time is not specified, Immunogenicity testing can be done at any time

13 Stored at -70 °C for follow-up exploration of pharmacodynamics, 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 ION-682884

Time (time is in reference to Study Drug administration):

a Pre-dose

b 24 hours

c 48 hours

d Pre-dose, 3 hours

e Pre-dose, 1, 2, 3, 4, 8 hours

f Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 hours

Appendix A Schedule of Procedures - Multiple-Dose Cohort D

	Screen	Baseline Assess-ments	Treatment Period[1] (13 Weeks)								Post-Treatment Evaluation Period[1] (13 Weeks)						
Study Week	-6 to -1	-6 to -1	1	2	3	5	7	9	11	13	14	15 or ET	17	19	21	23	26 or ET-FU
Study Day	-42 to -2	-42 to -1	1	8	15	29	43	57	71	85	92	99	113	127	141	155	176
Wisit Window (days) (+/-)	0	0	0	2	2	2	2	2	2	1	2	2	2	2	2	2	2
K)vemight Stay		X															
Informed Consent	X																
Inclusion/Exclusion	X	X															
Medical History	X																
I:)ody Weight and BMI	X											X					X
nyloid disease history	X																
ITTR Genotyping[2]	X																
Physical Exam[3]	X	X										X					X
r..;ital Signs[4]	X	X	X•	X	X	X•	X	X•	X	X•	X	X	X	X	X	X	X
HIV, Hepatitis B & C	X																
FSH[5]	X																
Pregnancy Test6	X	X					X					X			X		X
themistry Panel[7] KFasting[8])	X		X•	X	X	X•	X	X•	X	X•	X	X	X	X	X	X	X
Hematology[7]	X		X•	X	X	X•	X	X•	X	X•	X	X	X	X	X	X	X
Urinalysis	X		X•	X	X	X•	X	X•	X	X•	X	X	X	X	X	X	X
K)phthalmology Exam		X															X
ERG Exam		X															X
Retinol (Fasting[8])	X		X•			X•		X•		X•	X	X					X
PD Panel (Fasting[8])	X		X•	X	X	X•	X	X•	X	X•	X	X	X	X	X	X	X

Appendix A Schedule of Procedures - Multiple-Dose Cohort D *Continued*

	Screen	Baseline Assess-ments	Treatment Period[1] (13 Weeks)								Post-Treatment Evaluation Period[1] (13 Weeks)						
Study Week	**-6 to -1**	**-6 to -1**	1	**2**	3	**5**	7	**9**	**11**	**13**	**14**	**15** or ET	17	**19**	**21**	**23**	**26 or ET-FU**
Study Day	**-42 to -2**	**-42 to -1**	1	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**92**	**99**	**113**	**127**	**141**	**155**	**176**
Visit Window (days) (+/-)	0	0	0	**2**	**2**	**2**	**2**	**2**	**2**	**1**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
6-Minute Walk Test	X	X										X					
NYHA Classification/Score		X										X					
Transthoracic ECHO		X															
Cardiac MRI		X															
NT-proBNP	X		X•									X					
Troponin I		X	X•									X					
NIS	X																
mNIS+7[13]		2X										X					
Kansas City Cardiomyopathy Questionnaire		X										X					
EuroQoL-5 Dimension - 5 Level		X										X					
Nortolk QOL-DN[9]		X										X					
SF-36 Questionnaire			X•									X					
PND Score	X											X					
Compass-31 Autonomic Neuropathy Score		X										X					
Amyloidosis-Specific Qol questionnaire		X										X					

Appendix A Schedule of Procedures - Multiple-Dose Cohort D *Continued*

	Screen	Baseline Assess-ments	Treatment Period[1] (13 Weeks)								Post-Treatment Evaluation Period[1] (13 Weeks)						
Study Week	-6 to -1	-6 to -1	1	2	3	5	7	9	11	13	14	15 or ET	17	19	21	23	26 or ET-FU
Study Day	-42 to -2	-42 to -1	1	8	15	29	43	57	71	85	92	99	113	127	141	155	176
Wisit Window (days) (+/-)	0	0	0	2	2	2	2	2	2	1	2	2	2	2	2	2	2
Inflammatory Panel			X•		X	X•				X•		X					X
tomplement (C5a, Sb)			Xb			X				X•		X					X
PT, INR, aPTT	X		Xb			X				X•		X					X
ECG (12-Lead, triplicate)	X		XC							XC		X					X
hyroid Panel	X																
ION-682884 dministration			X			X		X		X							
dverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
oncomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK Blood Sampling[10, 11]			XC	X	X	X•	X	X•	X	XC	X	X	X	X	X	X	X
Immunogenicity Testing[11]			X•		X	X•						X					X
rchived Serum/Plasma amples[12]			X•	X	X	X•		X•	X	X•	X	X	X		X		X

Note: If not specifically labeled, "X" means any time
A 10-minute time window applies to all procedures to allow for flexbility where multiple procedures are scheduled at the same time

Appendix A Schedule of Procedures – Multiple-Dose Cohort D *Continued*

Legend *Continued*

1 Subjects who terminate early from the Treatment Period of the study should be encouraged to participate in the Post-Treatment Period. If the subject agrees, the subject should complete the Early Termination (ET) visit approximately 1-week after the last dose of ION-682884, followed by subsequent Post-Treatment visits. Subjects who terminate early from the Post-Treatment Period (and subjects who terminate early from the Treatment Period of the study and do not agree to participate in the Post-Treatment Period) should be encouraged to complete an ET visit

2 For determination of patient elig bility only if appropriate documentation is not available. In this case the tests may be conducted up to 10 weeks prior to Day 1. For biopsy, location per local practice.

3 Full physical exam to be given at Screening and abbreviated physical exam to be given during Treatment and Post-Treatment Period as indicated to assess changes from Screening

4 Blood Pressure (BP), heart rate (HR), respiratory rate (RR), temp

5 Women who are not surgically sterile as confirmation of menopause

6 Conducted only in women who are not surgically sterile. Dipstick acceptable at Day -1 only; all other pregnancy tests should be conducted on serum or plasma samples

7 If the platelet value, serum creatinine or liver enzyme tests are uninterpretable (e.g., due to clumping, hemolysis or quantity not sufficient) or missing a repeat blood specimen should be re-drawn as soon as possible (ideally within 7 days)

8 Fasted samples should be taken after fasting for at least 8 hours and preferably not more than 12 hours. During th s time the patient can drink water and they should ensure that they consume sufficient water in order to not become dehydrated

9 The Norfolk QOL-DN questionnaire must be administered prior to any other study procedures. During the baseline and EOT efficacy assessment periods, the Norfolk QOL-DN questionnaire should be administered on the same day as the first mNIS+7 assessment. The mNIS+7 assessment procedure includes the NIS, +7, NSC, and additional sensory and nerve conduction testing. If an ERG or ophthalmology examination are to be conducted on a mNIS+7 assessment day, the mNIS+7 assessment must be conducted first

- Two (2) independent mNIS+7 assessments will be performed at Baseline on separate days. Both assessments should be performed within 14 days prior to the first dose of ION-682884 (Day 1). In addition, every effort should be made to conduct the 2 assessments < 7 days apart

For an individual patient, every effort should be made to use the same mNIS+7 evaluator throughout the study and the evaluator must be insulated from the patient's general study procedures and knowledge of the patient's adverse events

10 See Appendix C for specific PK schedules

11 If time is not specified, Immunogenicity testing can be done at any time

12 Stored at -70 °C for follow-up exploration of pharmacodynamics, 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 ION-682884

Time (time is in reference to ION-682884 administration):

a Pre-dose

b Pre-dose, 3 hours

c Pre-dose, 1, 2, 3, 4, 6 hours

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 ION-682884 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
- Creatinine kinase
- Total IgG
- Total IgM

Screening Tests
- Hepatitis B surface antigen
- Hepatitis C antibody
- HIV antibody
- FSH (women only)
- Serum βhCG
- Drug/Alcohol screen

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

Complement
- C5a
- Bb

PD Panel
- Tranthyretin
- Retinol binding protein 4

Other
- Retinol
- Retinyl palmitate
- NT-proBNP
- Troponin I

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

Thyroid Panel
- TSH
- Free T4[4]
- Total T3[4]

Pharmacokinetics[1]
- ION-682884 in plasma
- ION-682884 in urine

Immunogenicity[2]
- Anti-ION-682884 antibodies

Inflammatory
- hs-CRP

Urinalysis
- Color
- Appearance
- Specific gravity
- pH
- P/C Ratio and A/C ratio
- Protein
- Blood
- Ketones
- Urobilinogen
- Glucose
- Bilirubin
- Leukocyte esterase
- Nitrate
- Microscopic examination[3]

1 Plasma, urine, and feces PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, immunogenicity testing (or possibly for purposes of immunogenicity assay development and/or validation) or to assess other actions of ION-682884 with plasma constituents

2 May be evaluated

3 Will be performed on abnormal findings unless otherwise specified

4 To be measured if TSH is outside of normal range

Appendix C PK Sampling Schedule for Single- and Multiple-Dose Cohorts

PK Sampling Schedule for Multiple-Dose Cohorts A, B and E

PK Sampling Schedule for Single-Dose Cohort C

PK Sampling Schedule for Multiple-Dose Cohort D

Appendix C PK Sampling Schedule for Single- and Multiple-Dose Cohorts

PK Sampling Schedule for Multiple-Dose Cohorts A, B and E

D1	D2	D3	D8	D15	D29	D43	D57	D71
Blood: Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours post-SC injection	Blood: 24 hours post-SC injection	Blood: 48 hours post-SC injection	Blood: Anytime	Blood: Anytime	Blood: Pre-dose	Blood: Anytime	Blood: Pre-dose	Blood: Anytime
Urine: 24-hour collection Feces: 24-hour collection[1]								

D85	D86	D87	D92	D99	D113	D127	D141	D155	D176
Blood: Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours post-SC injection	Blood: 24 hours post-SC injection	Blood: 48 hours post-SC injection	Blood: Anytime	Blood: Anytime	Blood: Anytime	Blood: Anytime	Blood: Anytime	Blood: Anytime	Blood: Anytime
Urine: 24-hour collection Feces: 24-hour collection[1]									

1 Fecal PK only to be collected for Cohort B

Note: SC = subcutaneous, D = Day

PK Sampling Schedule for Single-Dose Cohort C

D1	D2	D8	D15	D29	D50	D71	D92
Blood: Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours post-SC injection	Blood: 24 hours post-SC injection	Blood: Anytime	Blood: Anytime	Blood: Anytime	Blood: Anytime	Blood: Anytime	Blood: Anytime
Urine: 24-hour collection Feces: 24-hour collection							

Note: SC = subcutaneous, D = Day

Appendix C PK Sampling Schedule for Single- and Multiple-Dose Cohorts *Continued*

PK Sampling Schedule for Multiple-Dose Cohort D

D1	D8	D15	D29	D43	D57	D71
Blood: Pre-dose, 1, 2, 3, 4, and 6 hours post-SC injection	Blood: Anytime	Blood: Anytime	Blood: Pre-dose	Blood: Anytime	Blood: Pre-dose	Blood: Anytime

SC = subcutaneous, D = Day

D85	D92	D99	D113	D127	D141	D155	D176
Blood: Pre-dose, 1, 2, 3, 4, and 6 hours post-SC injection	Blood: Anytime	Blood: Anytime	Blood: Anytime	Blood: Anytime	Blood: Anytime	Blood: Anytime	Blood: Anytime

SC = subcutaneous, D = Day

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

Healthy Volunteers (Cohorts A, B, C and E)

hATTR Patients (Cohort D)

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

Healthy Volunteers (Cohorts A, B, C and E)

The following grading recommendations for adverse events relating to lab test abnormalities and adverse events at the injection site are based upon the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept. 2007.

Adverse Event	Mild	Moderate	Severe
Hematology			
aPTT prolonged	1.0 – 1.2 x ULN	>1.2 – 1.4 x ULN	> 1.4 x ULN
Eosinophils increased	650 – 1,500 cell/mm^3	1,501 - 5,000 cell/mm^3	>5,000 cell/mm^3
Fibrinogen decreased	150 – 200 mg/dL	125 – 149 mg/dL	< 125 mg/dL
Fibrinogen increased	400 – 500 mg/dL	501 – 600 mg/dL	> 600 mg/dL
Hemoglobin decreased Male Female	 12.5 – 13.5 g/dL 11.0 – 12.0 g/dL	 10.5 – 12.4 g/dL 9.5 – 10.9 g/dL	 < 10.5 g/dL < 9.5 g/dL
INR increased[†]	>1.2 - 1.5; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5; >1.5 - 2.5 x baseline if on anticoagulation; monitoring only indicated	>2.5; >2.5 x baseline if on anticoagulation; dose adjustment indicated
Lymphocyte count decreased	750 – 1,000 cell/mm^3	500 – 749 cell/mm^3	< 500 cell/mm^3
Neutrophil count decreased	1,500 – 2,000 cell/mm^3	1,000 – 1,499 cell/mm^3	< 1,000 cell/mm^3
Platelet count decreased	125,000 – 140,000 cell/mm^3	100,000 – 124,000 cell/mm^3	< 100,000 cell/mm^3
Prothrombin time (PT)	1.0 – 1.1 x ULN	>1.1 – 1.2 x ULN	> 1.2 x ULN
White blood cell decreased	2,500 – 3,500 cell/mm^3	1,500 – 2,499 cell/mm^3	< 1,500 cell/mm^3
White blood cell increased	10,800 – 15,000 cell/mm^3	15,001 – 20,000 cell/mm^3	>20,000 cell/mm^3
Chemistry			
Alanine aminotransferase increased[†]	>ULN - 3.0 x ULN if baseline normal 1.5 - 3.0 x baseline if baseline abnormal	>3.0 - 5.0 x ULN if baseline normal >3.0 - 5.0 x baseline if baseline abnormal	>5.0 x ULN if baseline normal >5.0 x baseline if baseline abnormal
Alkaline phosphatase increased	1.1 – 2.0 x ULN	>2.0 – 3.0 x ULN	> 3 x ULN

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

Healthy Volunteers (Cohorts A, B, C and E) *Continued*

Adverse Event	Mild	Moderate	Severe
Aspartate aminotransferase increased†	>ULN - 3.0 x ULN if baseline normal 1.5 - 3.0 x baseline if baseline abnormal	>3.0 - 5.0 x ULN if baseline normal >3.0 - 5.0 x baseline if baseline abnormal	>5.0 x ULN if baseline normal >5.0 x baseline if baseline abnormal
Blood bilirubin increased			
When accompanied by any increase in liver function test	1.1 – 1.25 x ULN	>1.25 – 1.5 x ULN	> 1.5 x ULN
When liver function test is normal	1.1 – 1.5 x ULN	>1.5 – 2.0 x ULN	> 2 x ULN
Blood urea nitrogen	23 – 26 mg/dL	27 – 31 mg/dL	>31 mg/dL
CPK increased*	>ULN - <6 ULN	6 - 10 x ULN	>10 x ULN
Creatinine increased	1.5 – 1.7 mg/dL	1.8 – 2.0 mg/dL	≥ 2.1 mg/dL
GGT increased†	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Hypercalcemia	10.5 – 11.0 mg/dL	11.1 – 11.5 mg/dL	≥ 11.6 mg/dL
Hyperglycemia††	Fasting glucose value ≥126 mg/dL (7.0 mmol/L)	Change in daily management to maintain fasting blood glucose <126 mg/dL (7.0 mmol/L); e.g. addition of oral antiglycemic agent; workup for diabetes	Insulin therapy initiated; hospitalization indicated
Hyperkalemia	5.1 – 5.2 mmol/L	5.3 – 5.4 mmol/L	≥5.5 mmol/L
Hypernatremia	144 – 145 mmol/L	146 – 147 mmol/L	≥148 mmol/L
Hypoalbuminemia	2.8 – 3.1 g/dL	2.5 – 2.7 g/dL	< 2.5 g/dL
Hypocalcemia	8.0 – 8.4 mg/dL	7.5 – 7.9 mg/dL	< 7.5 mg/dL
Hypoglycemia	65 – 69 mg/dL	< 64 mg/dL	Requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions‡
Hypokalemia	3.5 – 3.6 mmol/L	3.3 – 3.4 mmol/L	< 3.3 mg/dL
Hypomagnesemia	1.3 – 1.5 mg/dL	1.1 – 1.2 mg/dL	< 1.1 mg/dL
Hyponatremia	132 – 134 mmol/L	130 – 131 mmol/L	<130 mg/dL
Hypophosphatemia	2.3 – 2.5 mg/dL	2.0 – 2.2 mg/dL	< 2.0 mg/dL
Hypoproteinemia	5.5 – 6.0 g/dL	5.0 – 5.4 g/dL	< 5.0 g/dL
Lipase increased	1.1 – 1.5 x ULN	>1.5 – 2.0 x ULN	> 2 x ULN
Serum amylase increased	1.1 – 1.5 x ULN	>1.5 – 2.0 x ULN	> 2 x ULN

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

Healthy Volunteers (Cohorts A, B, C and E) *Continued*

Adverse Event	Mild	Moderate	Severe
Urine			
Proteinuria	Trace	1+	≥ 2+
Hematuria	1 - 10 cells per high power field	11 – 50 cells per high power field	> 50 cells per high power field
Adverse Events at the Injection Site			
Adverse events at the injection site**	An event at the injection site (e.g. erythema, tenderness, itching) that is easily tolerated by the subject and does not affect the subject's usual daily activities	- Persistent (>24 hours) pain, phlebitis or edema; OR - Lipodystrophy, hair growth or alopecia, OR - Prolonged (>1 month) hypo/hyperpigmentation	- Ulceration or necrosis; severe tissue damage; operative intervention indicated, OR - Any event at the injection site that is incapacitating

*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

†Grading for this parameter is derived from the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, November 27, 2017

††Modified for consistency with ADA "Standards of Medical Care in Diabetes - 2018" Diabetes Care 2018;41(Suppl. 1):S13–S27. https://doi.org/10.2337/dc18-S002

‡Modified for consistency with ADA "Glycemic Targets: Standards of Medical Care in Diabetes - 2018", Diabetes Care 2018;41(Suppl. 1):S55–S64. https://doi.org/10.2337/dc18-S006

**Grading for this parameter is adapted from the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, November 27, 2017

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

hATTR Patients (Cohort D)

The following grading recommendations for adverse events relating to lab test abnormalities and adverse events at the injection site are based upon the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, November 2017.

Adverse Event	Mild	Moderate	Severe
Hematology			
aPTT prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; bleeding
Eosinophils increased[1]	>ULN and >Baseline	-	Steroids Initiated
Fibrinogen decreased	<1.0 - 0.75 x LLN; if abnormal, <25% decrease from baseline	<0.75 - 0.5 x LLN; if abnormal, 25 - <50% decrease from baseline	<0.5 x LLN; if abnormal, ≥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	>1.2 - 1.5; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5; >1.5 - 2.5 x baseline if on anticoagulation; monitoring only indicated	>2.5; >2.5 x baseline if on anticoagulation; dose adjustment indicated
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 if baseline normal 1.5 - 3.0 x baseline if baseline abnormal	>3.0 - 5.0 x ULN if baseline normal >3.0 - 5.0 x baseline if baseline abnormal	>5.0 x ULN if baseline normal >5.0 x baseline if baseline abnormal
Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline normal 2.0 - 2.5 x baseline if baseline abnormal	>2.5 - 5.0 x ULN if baseline normal >2.5 - 5.0 x baseline if baseline abnormal	>5.0 x ULN if baseline normal >5.0 x baseline if baseline was abnormal
Alkalosis	pH >normal, but ≤7.5	-	pH >7.5
Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline normal 1.5 - 3.0 x baseline if baseline abnormal	>3.0 - 5.0 x ULN if baseline normal >3.0 - 5.0 x baseline if baseline abnormal	>5.0 x ULN if baseline normal >5.0 x baseline if baseline abnormal
Blood bilirubin increased	>ULN - 1.5 x ULN if baseline normal >1.0 - 1.5 x baseline if baseline abnormal	>1.5 - 3.0 x ULN if baseline normal >1.5 - 3.0 x baseline if baseline abnormal	>3.0 x ULN if baseline normal >3.0 x baseline if baseline abnormal
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*

hATTR Patients (Cohort D) *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**	>ULN - 1.5 x ULN if baseline normal > 1.0 - 1.5 x baseline if baseline abnormal	>1.5 - 3.0 x ULN if baseline normal >1.5 - 3.0 x baseline if baseline abnormal	>3.0 x ULN if baseline normal >3.0 x baseline if baseline abnormal
GGT increased	>ULN - 2.5 x ULN if baseline normal 2.0 - 2.5 x baseline if baseline abnormal	>2.5 - 5.0 x ULN if baseline normal >2.5 - 5.0 x baseline if baseline abnormal	>5.0 x ULN if baseline normal >5.0 x baseline if baseline abnormal
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 ≥126 mg/dL (7.0 mmol/L)	Change in daily management to maintain fasting blood glucose <126 mg/dL (7.0 mmol/L); e.g. addition of oral antiglycemic agent; workup for diabetes	Insulin therapy initiated; hospitalization indicated
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L; intervention initiated	>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; intervention initiated	>155 mmol/L; hospitalization indicated
Hyperphosphatemia	Laboratory finding only and intervention not indicated	Noninvasive intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated
Hyperuricemia	>ULN without physiologic consequences	-	>ULN 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‡	≥54 mg/dL - <70 mg/dL ≥3.0 mmol/L - <3.9 mmol/L	<54 mg/dL (3.0 mmol/L) AND no assistance required to actively administer carbohydrates, glucagon, or take other corrective actions	Requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions
Hypokalemia	<LLN - 3.0 mmol/L	symptomatic with <LLN - 3.0 mmol/L; 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	125-129 mmol/L and asymptomatic	125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms
Hypophosphatemia	Laboratory finding only and intervention not indicated	Oral replacement therapy indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 x ULN with signs or symptoms
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 x ULN with signs or symptoms

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

hATTR Patients (Cohort D) *Continued*

Adverse Event	Mild	Moderate	Severe
Urine			
Proteinuria Adults	1+ proteinuria; urinary protein ≥ULN - <1.0 g/24 hrs	2+ and 3+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs;	4+ proteinuria; 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 invasive intervention indicated
Adverse Events at the Injection Site			
Adverse events at the injection site**	An event at the injection site (e.g. erythema, tenderness, itching) that is easily tolerated by the subject and does not affect the subject's usual daily activities	- Persistent (>24 hours) pain, phlebitis or edema; OR - Lipodystrophy, hair growth or alopecia, OR - Prolonged (>1 month) hypo/hyperpigmentation	- Ulceration or necrosis; severe tissue damage; operative intervention indicated, OR - Any event at the injection site that is incapacitating

†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 ADA "Standards of Medical Care in Diabetes - 2018" Diabetes Care 2018;41(Suppl. 1):S13–S27. https://doi.org/10.2337/dc18-S002

‡Modified for consistency with ADA "Glycemic Targets: Standards of Medical Care in Diabetes - 2018", Diabetes Care 2018;41(Suppl. 1):S55–S64. https://doi.org/10.2337/dc18-S006

**Adapted from the original CTCAE V5.0 scale

Protocol

Version:	2
Version Date:	13 Jun 2019
Title:	A Phase 1/2 Stidu tp Evaluate the Safety, Tolerabilikty, Pharmacokinetics, and Pharmacodynamics of ION-682884, an Antisense Inhibitor of Transthreytin Production, in Healthy Volunteers and Patients with Transthyretin-Mediated

APPROVALS:

[redacted], 13-Jun-2019 21:45:48 GMT+0000

Official Title: A Phase 1/2 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of ION-682884, an Antisense Inhibitor of Transthyretin Production, in Healthy Volunteers and Patients with Hereditary Transthyretin-Mediated Amyloidosis

NCT Number: NCT03728634

Document Date: SAP Version 2: 07-April-2020

1.9 Documentation of Statistical Methods

Statistical Analysis Plan, Version 2.0 (06 April 2020), is provided.

Note to File – Revised Tables, Figures, and Listings

Statistical Analysis Plan

ION-682884-CS1

A Phase 1/2 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of ION-682884, an Antisense Inhibitor of Transthyretin Production, in Healthy Volunteers and Patients with Hereditary Transthyretin-Mediated Amyloidosis

Date: April 6, 2020

Version: 2.0

Statistical Analysis iPlan Signature Page

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Compound Name: [ON-'682884

Protocol: CSl

Study Title: A Phase 112Stndy to Evaluate the Safe1y, 'Dolerability, IPharmacokmetics. and Pharmaoodynamics ofION-682884, an Antisense Jnluoitor of Tr:anstbyretin Production. in Healthy Volunteers and Patients with Hereditary Transthyretin-Mediated Amyloidosis

Issue Date: 12 June 2019 (P:rotocolAmemlmenl2)

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PRIMARY RATIONALE FOR AMENDMENT

The following major modifications have been made to ISIS 682884 CSl SAP, version 1.0, dated 18 April 2019.

List of Major Modifications

Section	Title	Change/Rationale
1.1	Study Overview	Added Coho1t *EI* To reflect the changes in the Protocol Amendment 2. Removed the descriptions for Cohort D / It has been decided that the coho1t will not be conducted
3.4.3	Pha1macokinetic/Pha1macodynamic Exposure-Response Analysis	Update analysis method for exposure-response analysis
3.4.4	Metabolism	Add metabolism assessment and analysis plan
3.4.5	Immunogenicity (IM) Data Analysis	Add immunogenicity data analysis plan
3.6	Additional Analysis	Removed/ It has been decided the coho1t D will not be conducted

1. INTRODUCTION

This document provides a description of the study organization, study procedures, and the plan for the statistical analysis of the study data. Section 1 discusses study design, objectives, and endpoints; Section 2 provides the study procedures; Section 3 provides the detailed plan for the statistical analyses.

As with any statistical analysis plan (SAP), the proposed methods and approaches to the data analysis should be viewed as flexible. The statistical analysis to some degree is iterative since so much of the planning is based on statistical and other assumptions, which require verification.

1.1 Study Overview

This will be a Phase 1/2 study, consists of 2 portions. The healthy volunteer, Phase 1 portion will be a double-blind, randomized, placebo-controlled, dose-escalation study. It will be conducted at a single center and consist of 1 single-dose cohort and 2 planned multiple-dose cohorts (n = 12 per cohort, 10 active : 2 placebo). Approximately 36 healthy volunteers are planned to be enrolled. Twenty-four (24) subjects will be enrolled in the 2 planned multiple-dose cohorts and 12 subjects will be enrolled in the single-dose cohort. An additional multiple-dose cohort, Cohort E (n = 12), was added resulting in a total of approximately 48 healthy volunteers. The individual cohorts may be expanded to better assess the safety, tolerability, pharmacokinetic and pharmacodynamic of ION-682884 to meet study objectives. Maximum enrollment will be limited to 60 subjects in this portion.

The second portion of the study will be an open-label, multi-dose study in hATTR patients. It has been decided that this portion of the study, Cohort D (hATTR patient cohort), will not be conducted as planned. Therefore, the data analysis for Cohort D will not be performed.

Multiple-Dose Healthy Volunteer Cohorts

Cohort	Number of Doses	Total ION-682884
Cohort A: 45 mg ION-682884 or placebo SC	4	180 mg
Cohort B: 90 mg ION-682884 or placebo SC	4	360 mg

Subjects enrolled in the multiple-dose, healthy volunteer cohorts will receive SC doses of Study Drug once every 4 weeks for a total of 12 weeks (total of 4 doses). Following the administration of the 1st dose of Study Drug in each multiple-dose cohort, individual subjects must have completed their Day 15 safety evaluations with an acceptable safety profile, as determined by the Safety Committee, before receiving additional doses of Study Drug. Dosing in Cohort B can only proceed when at least 8 subjects in Cohort A have completed Day 29

safety evaluations and have demonstrated an acceptable safety profile as determined by the Safety Committee.

An additional multiple-dose, healthy volunteer cohort (Cohort E) with 4 every-4-week doses of 60 mg ION-682884 or placebo, was added to further elucidate safety and PD effects of ION-682884. Dosing in Cohort E can only proceed when at least 8 subjects in Cohort B have completed Day 29 safety evaluations and have demonstrated an acceptable safety profile as determined by the Safety Committee.

Cohort	Number of Doses	Total ION-682884
Cohort E: 60 mg ION-682884 or placebo SC	4	240 mg

The length of each subject's participation in the multiple dose cohorts (Cohorts A, B, and E) is approximately 29 weeks, including a 4-week Screening Period, a 12-week Treatment Period, and a 13-week Post-Treatment Evaluation Period. Subjects will receive a total of 4, once every 4 weeks, fixed SC doses of ION-682884.

Single-Dose Healthy Volunteer Cohort

Cohort	Number of Doses	Total ION-682884
Cohort C: 120 mg ION-682884 or placebo SC	1	120 mg

Dosing in Cohort C can only proceed when at least 8 subjects in Cohort A have completed Day 57 safety evaluations and have demonstrated an acceptable safety profile as determined by the Safety Committee. Subjects enrolled in the single-dose treatment cohort will receive a single SC dose of the Study Drug (ION-682884 or placebo) on Day 1.

For each multiple-dose or single-dose healthy volunteer cohort, the first 2 (sentinel) subjects (randomized 1 active:1 placebo) will be dosed on the same day. If no major safety concerns are observed following 48 hours of observation, as determined by the Safety Committee, dosing of the remaining 10 subjects (randomized 9 active:1 placebo) in that cohort may proceed.

The length of each subject's participation in the single dose cohort (Cohort C) is approximately 17 weeks, including a 4-week Screening Period, a single-dose on Day 1 and 13 weeks of Post-Treatment Follow-up. Subjects will return for outpatient visits as outlined in protocol Appendix A.

hATTR Patient Cohort

It has been decided that Cohort D (hATTR patient cohort) will not be conducted.

1.2 Objectives

1.2.1 Primary Objectives

To evaluate the safety and tolerability of single and multiple doses of ION-682884 administered subcutaneously to healthy volunteers and patients with hATTR.

1.2.2 Secondary Objectives

To evaluate the pharmacokinetic and pharmacodynamic profiles of single and multiple doses of ION-682884 administered subcutaneously to healthy volunteers and patients with hATTR.

1.2.3 Exploratory Objectives

To evaluate the effects in hATTR patients of multiple doses of ION-682884 on the mNIS+7, Norfolk QoL, 6MWT, 10MWT, EQ-5d, SF-36, COMPASS, and Amyloidosis-specific QoL.

Since Cohort D (hATTR patient cohort) will not be conducted, the corresponding objectives and endpoints for the cohort will not be evaluated.

1.3 Endpoints

1.3.1 Primary Endpoints

Analysis of safety labs, AEs, concomitant medications, ECG and physical examinations of healthy volunteers and patients with TTR amyloidosis following subcutaneously administration of single and multiple doses of ION-682884.

1.3.2 Secondary Endpoints

1.3.2.1 Pharmacokinetic Endpoints

The plasma pharmacokinetics of ION-682884 will be assessed following single and multiple SC administration(s). The amount of ION-682884 excreted in urine over selected 24-hour collection intervals will be determined, and metabolite identification and profiling may also be determined in some of the collected plasma, urine, and fecal samples, at a later time.

1.3.2.2 Pharmacodynamic Endpoints

Analysis of pharmacodynamic data will determine the change and percent change from Baseline in plasma TTR and RBP4 levels following single- and multiple-dose SC administration of Study Drug.

1.3.3 Additional/Exploratory Endpoints

Exploratory endpoints for the open-label, hATTR patient cohort are the change from Baseline to Week 14 or Week 15 in the following:

- Modified neuropathy impairment score +7 (mNIS +7) score
- Norfolk quality of life-diabetic neuropathy (Norfolk QOL-DN) questionnaire total score
- 6 Minute walk test (6MWT)
- 10 Meter Walk Test (10-MWT)
- EuroQoL-5 Dimensions (EQ-5d)
- SF-36 physical functioning domain and physical component score
- COMPASS-31 autonomic neuropathy questionnaire
- Amyloidosis-specific QoL questionnaire

Since Cohort D (hATTR patient cohort) will not be conducted, the exploratory endpoints described in this section will not be evaluated.

2. PROCEDURES

2.1 General Overview of Procedures

Ionis Pharmaceuticals, Inc. will review all study data including source documents, CRFs, and laboratory reports. The study site will enter subject source data into the case report form. Central laboratory data will be transferred electronically to Ionis Pharmaceuticals, Inc.

2.2 Randomization & Treatment Allocation

Subjects will be randomized (Cohorts A, B, E and C) after all Baseline and Screening assessments have been completed and after the Investigator has verified that they are eligible per criteria in protocol Sections 5.1 and 5.2 (Cohorts A, B, E and C). No subject may begin treatment prior to randomization or registration and assignment of a unique subject identification number.

For Cohorts A, B, E and C, within each cohort, subjects will be randomized 10:2 to receive ION-682884 or placebo as outlined in protocol Section 3.1. The randomization list will be prepared by an independent external vendor.

2.3 Conduct

The study will be conducted in accordance with current Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) guidelines, the World Medical Association Declaration of Helsinki guidelines, the Food and Drug Administration (FDA) Code of Federal Regulations, and all other local regulatory requirements.

2.4 Data Monitoring

2.4.1 Safety Data Monitoring

Ionis Pharmaceuticals, Inc. (or designee) is responsible for processing all reported adverse events (AEs). All serious adverse events (SAEs), reported to Ionis Pharmaceuticals, Inc. (or designee), are reviewed according to standard operating procedures. The medical monitor will review all AEs and SAEs on an ongoing basis throughout the study. Ionis Pharmaceuticals, Inc. (or designee) will prepare and submit safety reports to the health authorities worldwide in accordance with local requirements. If it becomes necessary to communicate new safety information, Ionis Pharmaceuticals, Inc. (or designee) will also prepare a safety notification letter and transmit it to study site.

2.5 Data Management

An electronic case report form (eCRF) utilizing an Electronic Data Capture (EDC) application will be used for this Study.

2.5.1 Case Report Form Data

BioClinica (or designee) is responsible for creating the Electronic Data Capture (EDC) data entry screens, database and edit checks using definitions developed by Ionis Pharmaceuticals, Inc. Ionis Pharmaceuticals, Inc. is responsible for the review, data management querying and locking of the database.

Data are single-entered into the EDC system by the site staff. Programmed edit checks (computer logic that checks the validity of the data entered and also prompts for missing data that is expected to be entered) are run and automatic queries are generated. Ionis Pharmaceuticals, Inc. reviews all data for accuracy and validity and generates additional queries in the EDC system when necessary. The data is corrected or an explanation concerning the query is provided in the EDC system. After all data are entered, reviewed (by Data Management and Clinical Development) and queried, and all queries resolved, the database is locked.

2.5.2 Laboratory Data

Ionis Pharmaceuticals, Inc. is responsible for the format of the laboratory electronic data transfers, transfer schedule and review of the clinical laboratory data. This lab data will be stored as SAS data sets or Excel files.

2.5.3 Pharmacokinetic Data

Ionis Pharmaceuticals, Inc. is responsible for the management and review of the plasma and urine drug concentration data. Final data, which has been approved by Quality Assurance, will be stored in controlled repository.

3. ANALYTICAL PLAN

3.1 General Overview of Analyses

3.1.1 Statistical Methods

Descriptive summary statistics including number of subjects, 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. All statistical tests will be conducted using 2-sided tests with 5% Type I error rate unless otherwise stated. In view of the exploratory nature of this study, adjustments for multiplicity of testing will generally not be used.

Both central and local lab data will be used in platelet analyses, including by visit summaries/figures and abnormality summary. For other lab tests, only central laboratory data will be used.

PK parameters will be summarized using number of subjects, mean, standard deviation, coefficient of variation (CV), geometric mean, geometric %CV, median, minimum, and maximum.

The placebo subjects in the multiple-dose healthy volunteer cohorts (Cohorts A, B, and E) will be pooled.

The summaries will be presented separately for:

- Single-dose healthy volunteer cohort (Cohort C)
- Multiple-dose healthy volunteer cohorts (Cohorts A, B, and E)

Baseline definition

For ECG, baseline for numeric results will be defined as the average of the triplicates taken on Day 1 Pre-dose, if more than one time point is taken on Day 1 pre-dose, all non-missing assessments (time points and replicates) will be averaged as the baseline value. Baseline for character results will be defined as the worst of Day 1 Pre-dose assessments.

For platelet count, baseline will be defined as the average of all non-missing pre-dose assessments, including unscheduled visits.

For other assessments, when 2 or more measurements are obtained prior to the subject or patient receiving their first dose of Study Drug, baseline will be defined as the average of the pre-dose measurement closest to Day 1 and Day 1 pre-dose. Day 1 pre-dose is the Day 1 measurement taken prior to the time of the first dose. Otherwise baseline will be defined as the

last non-missing measurement prior to the date and time of the first dose of Study Drug (ION-682884 or placebo).

Analytical visits:

Data will be summarized using the visit labels provided in the data. Multiple results with the same visit label will be averaged. Results with visit labels as "Unscheduled" or "Early Termination Follow-up" will not be included in the by-visit summary tables and figures except for determining baseline and laboratory abnormality summaries, but will be presented in data listings.

3.1.2 Subject Population Analyzed

The following analysis populations will be used for the analysis of data as described within each analysis population.

Full Analysis Set: All randomized subjects (Cohorts A-C, E) who receive at least 1 injection of Study Drug (ION-682884 or placebo).

Per Protocol Set: Subset of the Full Analysis Set that have received at least 3 doses of Study Drug (1 for the single-dose healthy volunteer cohort) and that have no significant protocol deviations that would be expected to affect efficacy assessments.

Safety Set: All randomized subjects (Cohorts A-C, E) who receive at least 1 injection of Study Drug.

Pharmacokinetic Set: All subjects who are randomized and receive at least 1 dose of active Study Drug (ION-682884) and have at least 1 evaluable PK sample.

In addition to the above analysis populations, it is recognized that some data displays will be provided for "All Screened", "Screening Failures" and "All Randomized" subjects but no data analysis will be executed in these populations except for the disposition table that includes all screened subjects.

3.1.3 Sample Size Consideration

There is no statistical rationale for the selected sample size of the single-dose and multiple-dose treatment cohorts. The sample size was based on prior experience with second generation ASOs in healthy volunteers to ensure that the safety, tolerability, PK, and preliminary PD of ION-682884 will be adequately assessed while minimizing the unnecessary subject exposure.

3.1.4 Planned Interim Analysis

Unblinded analyses may be conducted after completion of dosing in each healthy volunteer cohort.

3.1.5 Incomplete or Missing Data

Missing values will not be imputed unless otherwise specified

3.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics (e.g., age, gender, race, height, weight, BMI, TTR type) will be summarized using descriptive statistics by treatment group.

For race summary, if multiple races were recorded in database, 'Multiple Race' will be used in the summary table, details will be provided in the listing.

Medical history will be provided in the data listings.

Subject enrollment and disposition will be summarized for each treatment group and for all subjects. The summaries will include: the total number of screened subjects, the number of randomized or registered subjects, the number of subjects in each analysis set (with the exception of the PK Set), the number of subjects completing treatment, the primary reason for terminating treatment, the number of subjects completing post-treatment follow-up, and the primary reason for terminating post-treatment follow-up.

3.3 Safety Analyses

The safety analysis will be conducted on the Safety Set.

3.3.1 Adverse Events

An adverse event will be regarded as treatment emergent if it is present prior to receiving the first dose of Study Drug and subsequently worsens, or is not present prior to receiving the first dose of Study Drug but subsequently appears.

If there is no "Formlink" link, and the AE (start date/time) occurs after the subject's first dosing date/time, then the AE is treatment-emergent. Otherwise, if the AE (start date/time) occurs prior to the subject's first dosing date/time, then the AE is not treatment-emergent.

If there is a "Formlink" link between two AE records, the records will be compared as a pair, and consider two cases, where the AE severity (mild/moderate/severe) will be compared between the two records in the pair. The 2 records will be chronologically ordered by AE start date and referred to as the "first" and "second" AEs.

Case 1: The first AE record in the pair occurs <u>before</u> first dosing, and the second record occurs <u>after</u> dosing.

If the AE severity on the second record is worse than the severity on the first record, then only count the second AE as treatment-emergent. But, if the severity improves (second record

severity is less severe than the first record severity), then neither record is counted as treatment-emergent.

Case 2: Both AE records in the pair occur after first dosing.

If the AE severity on the second record is worse than the severity on the first record, then count both records as treatment-emergent. But, if the severity improves, then only count the first record as treatment-emergent.

When counting the total number of treatment-emergent events, events linked together through change in severity will still be counted as separate events.

The most conservative approach will be used to determine if the event occurs after treatment. For example, if the onset date or resolution date of an AE is prior to the first study treatment date, it will be considered to have occurred prior to the study period. If the onset or resolution date of an AE is a partial date with only month or year available or completely missing, then the event is assumed to be within the study period unless the year is prior to the year of the first study treatment date, or if in the same year, the month is prior to the month of the first study treatment date.

The incidence of AEs will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) (version 21.1) preferred term and system organ class for:

- Any treatment emergent adverse events
- Related treatment emergent adverse events. Related is defined as “Related”, “Possible”, or missing relationship to study drug
- Any treatment emergent adverse events by severity. At each level of patient summarization, a patient is classified according to the highest severity if the patient reported one or more events. Adverse events with missing severity will categorized as “Missing” for this summary
- Related treatment emergent adverse events by severity
- Serious treatment emergent adverse events
- Serious and related treatment emergent adverse events

AEs that lead to study discontinuation or investigational drug discontinuation will be listed. Non-treatment emergent adverse event will be flagged in the data listing.

Local Cutaneous Reactions at the Injection Site

Local cutaneous reaction at injection site (LCRIS) is defined as adverse events with the preferred terms (PTs) Injection site erythema, Injection site swelling, Injection site pruritus, or Injection site pain that started on the day of injection, persisted for at least two days or ongoing. Events with onset date on the day of injection and missing resolution date will also be included.

The number and percent of patients in each treatment group experiencing LCRIS will be tabulated.

Percentage of injections leading to LCRIS will also be summarized. Percentage of injections leading to LCRIS will be calculated for each patient as (A/B)*100, where A is the number of injections with LCRIS, and B is the total number of injections.

LCRIS will be listed.

Flu-like Reactions

Flu-like reaction (FLR) is defined as adverse events with PTs including either (A) Influenza like illness or (B) Pyrexia or Feeling hot or Body temperature increased, plus at least two of the following symptoms with the PTs: Chills, Myalgia, or Arthralgia, starting on day of injection or the next day.

FLRs will be summarized using the MedDRA coding system, by preferred term.

Percentage of injections leading to FLRs will be summarized by treatment group using the descriptive statistics.

Percentage of the injections leading to FLRs will be calculated as follows for each patient: (A/B)*100, where A=number of injections leading to FLRs, and B=total number of injections.

FLRs will be listed.

3.3.2 Laboratory Measurements

The following is the list of lab analytes that will be collected throughout the study:

- Chemistry: sodium, potassium, chloride, bicarbonate, total protein, albumin, calcium, magnesium, phosphorus, BUN, creatinine, uric acid, total bilirubin, direct (conjugated) bilirubin, indirect (unconjugated) bilirubin, ALT, AST, alkaline phosphatase, creatinine kinase, total IgG, and total IgM
- Hematology: red blood cells, hemoglobin, hematocrit, MCV, MCH, MCHC, RDW, MPV, platelets, white blood cells, and wBC differential (percentage and absolute count) (basophils, eosinophils, lymphocytes, monocytes and neutrophils)
- Coagulation: aPTT, PT, INR

- Complement: Bb, C5a
- Thyroid Panel: TSH, free T4, total T3. The data will only be displayed in subject listings.
- Screening Tests: hepatitis B surface antigen, hepatitis C antibody, HIV antibody, FSH (women only, if applicable), serum βhCG (women only) and Drug/alcohol screen. The data will only be displayed in subject listings.
- Inflammatory: hs-CRP.
- Urinalysis: color, appearance, specific gravity, PH, P/C ratio, A/C ratio, protein, blood, ketones, urobilinogen, glucose, bilirubin, leukocyte esterase, nitrate, microscopic examination. The numeric results will be summarized.

All lab data will be displayed in subject listings.

Chemistry, hematology, coagulation, complement, inflammatory, and urinalysis (result, change and percent change from baseline) will be summarized using descriptive statistics (n, mean, median, standard error, standard deviation, Q1, Q3, minimum, and maximum) by treatment group and study visit.

For ALT and AST, the number and percent of subjects falling in each of the following categories based on the confirmed results will be tabulated by treatment group:

- ALT/AST > 3 x ULN, which is confirmed
- ALT/AST > 5 x ULN, which is confirmed

For platelet count, the number and percentage of subjects falling in each of the following categories based on the confirmed results will be tabulated by treatment group: 100,000/mm^3 to <140,000/mm^3, 75,000 to <100,000/mm^3, 50,000 to <75,000/mm^3, 25,000 to <50,000/mm^3, 0 to <25,000/mm^3, which is confirmed.

A confirmed value is based on a consecutive lab value within 7 days. If that value is in the same or worse category the initial value is confirmed. If the consecutive value is in a better category, then the initial value is confirmed using the consecutive value category. If there is no retest within 7 days, then the initial value is presumed confirmed. If there are multiple results on the same day, no matter from the same lab vendor or different lab vendors, then the worst value will be utilized in the analysis.

3.3.3 Vital Signs, Weight, and BMI

Vital signs will include heart rate, respiratory rate, body temperature, systolic and diastolic blood pressure. Summary tables will be created to present the descriptive statistics (n, mean, standard error, standard deviation, median, Q1, Q3, minimum, and maximum) for vital sign

values, weight, BMI as well as the change and percent change from baseline at each study visits.

3.3.4 Physical Examinations

Adverse changes in physical examinations that are deemed clinically significant by the Investigator will be classified as adverse events. All physical examination data will be provided in a data listing.

3.3.5 12-Lead Electrocardiograms (ECG)

The ECG data will include ventricular rate, PR interval, QRS duration, QT, QTcF (QT corrected using the Fridericia's formula), QTcB (QT corrected using the Bazett's formula), and Overall interpretation. QTcF and QTcB will be calculated based on the subject's reportable ECG data at each time point using the formula described below:

$QTcF = QT / (RR)^{1/3}$, where RR= 60/VR

$QTcB = QT / (RR)^{1/2}$, where RR= 60/VR

QTcF and QTcB will be calculated from each ECG triplicate measurement. The machine-specific QTcB values (recorded from ECG machine on the CRF) will not be summarized.

Summary tables will be created to present the descriptive statistics for ECG parameters as well as the change and percent change from baseline at each study visits. For triplicates or multiple results at same visit, the average will be used in the summary.

For the categorical data, counts and percentages will be provided. For triplicates or multiple results at the same visit, the worst case result will be used in the summary.

3.3.6 Concomitant Medications

Concomitant medications will be coded using WHO Drug dictionary (version Global B3 September 2018) and summarized by ATC class, generic name and treatment group.

3.4 Pharmacokinetic Analysis

The plasma pharmacokinetics of ION-682884 (measured as total full-length oligonucleotides or ION-682884-equivalent, i.e., ION-682884-eq, including fully conjugated, partially conjugated, and unconjugated ION-682884), will be assessed following SC administration. The amount of ION-682884-eq excreted in urine over selected 24-hr collection intervals will be determined following single and multiple SC administrations.

Data from metabolite identification and profiling in some of the collected plasma, urine, and fecal samples will be reported either in the CSR or separately, if the samples are analyzed at a later time.

3.4.1 Plasma Pharmacokinetics

3.4.1.1 Plasma Concentration Data of Total Full-Length Oligonucleotides

Plasma concentrations of ION-682884-eq., along with the scheduled (nominal) and actual samples times (i.e., time from SC dosing) will be listed for each subject, by treatment group, dose cohort, nominal dose, and day. In addition, percent differences between scheduled and actual sampling times will also be listed for all subjects.

Plasma concentrations below the lower limit of quantification (LLOQ) will be indicated by "BLQ". For the purpose of calculating typical descriptive statistics (n, mean, SD, %CV, geometric mean, geometric %CV, median, minimum, and maximum) for plasma concentrations, all BLQ values will be set to zero. Mean plasma concentrations that are BLQ will be presented as BLQ, and the SD, %CV, geometric mean, and geometric %CV, will be reported as not applicable. Summary statistics of the ION-682884 plasma concentrations will be tabulated by treatment group, dose cohort, nominal dose, day, and scheduled time point. At the discretion of the pharmacokineticist and/or biostatistician, samples may be excluded from descriptive statistics if there are large deviations between scheduled and actual sampling times, or large deviations between actual dose and nominal dose.

ION-682884-eq. plasma concentration versus time (actual) profiles for each subject that received ION-682884 active treatment, as well as the median plasma concentrations versus time (scheduled) profiles in both single- and multiple-dose cohorts, will be presented graphically on linear and/or semilogarithmic scales. At the discretion of the pharmacokineticist and/or biostatistician, samples may be excluded from the median plots if there are large deviations between scheduled and actual sampling times.

3.4.1.2 Plasma Pharmacokinetic Parameters

Non-compartmental pharmacokinetic analysis of ION-682884-eq. will be carried out on each individual subject data set using Phoenix WinNonlin Version 8 or higher (Certara L.P., Mountain View, CA). Plasma pharmacokinetic parameters in each subject (when applicable) will be determined. For calculation of PK parameters, all BLQ values will be set to zero. The following plasma PK parameters for ION-682884-eq. will be calculated (when applicable and not necessarily limited to) and based on actual sampling times:

- C_{max}: the maximum observed ION-682884-eq. concentration in plasma.
- T_{max}: the time at which C_{max} occurs.
- $AUC_{0\text{-}24h}$: partial areas under the plasma concentration-time curve from zero time (pre-dose) to 24 hours will be calculated using the linear up-log down trapezoidal rule
- AUC_{last}: partial areas under the plasma concentration-time curve from zero time (predose) to the last quantifiable concentration (T_{last}) using $C_{observed}$ will be calculated

using the linear up-log down trapezoidal rule for the single-dose cohort (i.e., Cohort C) only.

- $AUC_{0-\infty}$: area under the plasma concentration-time curve (AUC) from time zero to the last quantifiable concentration (AUC_{last}) with extrapolation to infinity observed will be calculated using the linear up-log down trapezoidal rule. This parameter will be calculated for the single-dose cohort (i.e., Cohort C).
- $\%AUC_{extr}$: percentage of extrapolated area under the curve from T_{last} to infinity, expressed as percentage of $AUC_{0-\infty}$. This parameter will be calculated for Cohort C only.
- AUC_{0-672h} (i.e., AUC_{τ}): partial area under the plasma concentration-time curve (AUC) over a dosing interval (i.e., from time zero to 672 hours), will be calculated using the linear up-log down trapezoidal rule, as appropriate.
- CL/F: Apparent plasma clearance after SC administration. This parameter will be calculated as CL/F = Actual Dose/$AUC_{0-\infty}$ for Cohort C only.
- CL_{0-24h}/F: Apparent plasma clearance from time zero to 24 hours after SC administration. This parameter will be calculated as CL_{0-24h}/F = Actual Dose/AUC_{0-24h}.
- CL_{ss}/F: Apparent plasma clearance at steady-state after SC administration. This parameter will be calculated as CL_{ss}/F = Actual Dose/AUC_{τ} following the last dose in the MD cohorts only.
- $t_{1/2\lambda z}$: apparent terminal elimination half-life will be calculated from the equation, $t_{1/2\lambda z} = 0.693/\lambda_z$, where λ_z is the rate constant associated with the apparent terminal elimination phase. This parameter will be calculated for Cohort C (if data permitted) and following the last dose in the MD cohorts, as appropriate.
- V_z/F: Apparent volume of distribution in the terminal phase will be calculated from $V_z/F = CL_{ss}/F/\lambda_z$. This parameter will be calculated for Cohort C and following the last dose in the MD cohorts, as appropriate.

λ_z shall be determined over a time interval equal to at least 1.5 x $t_{1/2\lambda z}$. A minimum of three data points in the elimination phase will be used to calculate λ_z using log-linear regression analysis and the adjusted correlation of determination values (r^2_adj) shall be at or greater than 0.8 for the estimate to be accepted. If at least one of these three conditions are not fulfilled, the PK parameters depending on λ_z (i.e., $AUC_{0-\infty}$, $\%AUC_{extr}$, $t_{1/2\lambda z}$, and V_z/F) shall be flagged as not reliable if calculated and listed. They will generally be excluded from descriptive statistics and statistical testing procedures, or at the discretion of the pharmacokineticists, who are in charge of the PK analysis.

Plasma pharmacokinetic parameters will be summarized using descriptive statistics (n, mean, SD, %CV, geometric mean, geometric %CV, median, minimum, and maximum) by treatment group, dose cohort, nominal dose, and day. Additionally, the relationship between dose and plasma exposure parameters (C_{max} and AUC) of total full-length ASOs (ION-682884-eq.) will be evaluated using linear-regression analysis of the log-transformed mean data.

3.4.2 Urinary Excretion

The amount and percentage of the administered dose excreted in urine as total full-length oligonucleotides (ION-682884-eq.) following 0 to 24-hour collection will be calculated using the following equation on Day 1 in single-dose cohorts, and following the first and last dose in multiple-dose cohorts:

$$Ae_{0\text{-}24h} = C_{urine} \times V_{urine}$$

Where, $Ae_{0\text{-}24h}$ is the amount excreted up to 24 hours, C_{urine} is the urine concentration of ION-682884-eq., and V_{urine} is the total urine volume. The percentage of the administered dose excreted in urine (as ION-682884) will then be calculated from the following expression:

$$\% \text{ Dose Excreted} = (Ae_{0\text{-}24h} \div \text{Administered Dose}) \times 100\%$$

Renal clearance (CL_r) will also be determined from the following expression:

$$CLr = \frac{Ae_{0\text{-}24h}}{AUC_{0\text{-}24h}}$$

Urinary excretion PK parameters will be summarized using descriptive statistics (n, mean, SD, %CV, geometric mean, geometric CV%, median, minimum, and maximum) by treatment group, cohort, nominal dose and day. At the discretion of the pharmacokineticist and/or biostatistician, urinary excretion PK parameters may be excluded from the statistical summary if the collection interval is less than 16.8 hours (i.e., <30% of planned collection interval) and/or missing collection interval.

3.4.3 Pharmacokinetic/Pharmacodynamic Exposure-Response Analysis

Exposure-response relationship may be explored graphically between plasma trough and post-treatment concentrations, and selected PD measures (e.g., TTR level and/or %baseline), if the data deemed appropriate.

Population PK and PKPD analysis may be performed using the PK and PD data from this study, and/or combined with other clinical study data and reported separately in the future.

3.4.4 Metabolism

A subset of plasma, urine, and fecal samples collected from the study will be further analyzed using a non-validated HPLC-MS/MS method to characterize and profile the relative abundance

of each full-length oligonucleotide species, including parent compound ION-682884, ION-682884 with 1, 2, and/or 3GalNAc sugar deletions, and unconjugated ION-682884. Evaluation of oligonucleotide metabolites of ION-682884 (shortmer metabolites) will be conducted using a non-validated HPLC-UV-MS method. Lastly, the presence of ION-682884 linker-related metabolites will be characterized in a subset of the collected plasma, urine, fecal samples using a non-validated HPLC-MS/MS method.

For metabolism data associated with identification and characterization of the concentrations and relative abundance of each full-length oligonucleotide species, including fully conjugated ION-682884, ION-682884 with 1, 2, and/or 3 GalNAc sugar deletions, and unconjugated ION-682884, concentrations of total full-length oligonucleotides will be calculated by the sum of molar concentrations of each full-length oligonucleotide species (including fully conjugated, partially conjugated, and unconjugated ION-682884) for each sample collected for metabolite identification and profiling. Relative abundance of each full-length oligonucleotide species in the sample will be calculated as the molar concentration each full-length oligonucleotide species divided by the molar concentrations of the total full-length oligonucleotides and expressed as percentage. Concentrations and relative abundance of each full-length oligonucleotide species will be summarized by limited descriptive statistics (n, mean, and SD). All BLQ values will be set to zero when calculating descriptive statistics. Percent abundance of each full-length oligonucleotide species will not be calculated if all the full-length oligonucleotide species in the sample are BLQ.

Data from profiling of length-based oligonucleotide metabolites associated with nuclease-mediated metabolism (shortmer oligonucleotide metabolites), i.e., percent peak areas, as well as characterization of linker-related metabolites, will reside in their respective bioanalytical reports, and may be summarized using limited descriptive statistics if deemed necessary.

3.4.5 Immunogenicity (IM) Data Analysis

Samples collected Days 1, 15, 29, 92/99, and 176, including early termination samples from both single and multiple dose cohorts, will be analyzed for anti-ION-682884 antibodies (ADA) to evaluate ION-682884 immunogenicity. Samples for IM assessment were collected prior to dosing if the subject received a study drug administration on the day of IM sample collection.

3.4.5.1 Sample Level ADA Data

An evaluable sample will be designated ‘Positive’ based on both positive screening and confirmation assay results (i.e., confirmed positive result), and otherwise will be deemed ‘Negative’. Sample ADA results (screen positive/negative, confirmed positive/negative, or unevaluable (“Unknown”), and when applicable, titer of anti-ION-682884 antibodies) before,

during, and after treatment with study drug (ION-682884 or placebo) (sample ADA status) will be listed by treatment, dose, and day of collection.

The sample ADA incidence (number) and incidence rate (percent) at each evaluated study day will be determined and appropriately summarized by treatment and dose as the total number of and percentage of evaluated subjects with sample ADA negative, positive, and unknown status.

3.4.5.2 Subject Level ADA Data

Subject ADA status overall (ADASTAT) will be defined as "Positive" status if they have at least one confirmed positive sample result at any time during the treatment or post-treatment evaluation periods; "Negative" status if all evaluated ADA sample results during the treatment and post-treatment evaluation periods are ADA negative and they have at least one evaluable ADA result collected post study drug treatment. Otherwise, a study subject will be assigned "Unknown" subject ADA status.

Furthermore, subjects with positive overall ADA status will be further classified into different ADA types (ADATYPE) based on their baseline ADA status and the change in ADA titer between pre- and post-treatment as described below (Shankar et al.,2014):

- Treatment-Induced ADA: ADA developed de novo (seroconversion) following biologic drug administration (i.e., formation of ADA any time after the initial drug administration in a subject without pre-existing ADA, i.e., baseline negative ADA)
- Treatment-Boosted ADA: Pre-existing ADA that were boosted to a higher level following biologic drug administration (i.e., any time after the initial drug administration the ADA titer is greater than the baseline titer by a factor of 4-fold or more)
- Treatment-Unboosted ADA: Pre-existing ADA that are not boosted following biologic drug administration (i.e., any time after the initial drug administration the ADA titer is less than 4-fold of the baseline titer)
- ADATYPE would be not applicable (NA) if the subject overall ADA status is negative.

Other subject level IM parameters to be calculated/defined will include but may not limited to:

- Subject ADA Status at Baseline (ADASTATB): "Positive" if the subject has Week 1 Day 1 pre-dose sample (baseline) is confirmed positive; "Negative" if the subject has Week 1 Day 1 pre-dose sample (baseline) is confirmed negative; "Unknown" if the subject has Week 1 Day 1 pre-dose sample (baseline) unevaluable.

- Onset of ADA (TFSTADA): i.e., the first day ADA positive sample observed, will be calculated by: the date of first sample has "positive" sample IM status - first dose date +1
- Last Positive ADA Study Day (TLSTADA): defined as the last positive ADA sample observed from the start of study drug treatment and will be calculated by: the date of last sample has "positive" sample IM status - first dose date +1
- Last IM Sampling Study Day (TLSTSAMP): defined as the last ADA sample collected from the start of study drug treatment and will be calculated by: the date of last sample collected - first dose date +1
- Peak titer (PEAKTIT): the highest titer observed for the subject
- Time to peak titer (TPEAKTIT): the time to reach peak titer will be calculated by: the date of first peak titer observed- first dose date +1
- Total number of ADA Positive Samples (NOPOSAMP): the total number of ADA samples being confirmed positive for the subject
- Total number of ADA Samples evaluated (NOADASAMT): the total number of ADA samples being collected and analyzed successfully with reportable results for the subject
- Percentage of Positive Samples (PCPOSAMP): the percentage of ADA samples being confirmed positive for the subject and will be calculated by:

$$\text{PCPOSAMP (\%)} = 100 \times \frac{\text{NOPOSAMP}}{\text{NOADASAMT}}$$

Lastly, subjects with positive ADA status may further be classified as being transient or persistent ADA response, if there are sufficient number of subjects with transient ADA status. Transient and persistent ADA definitions are defined below and based on Shankar et al. (2014):
Transient ADA response:

- Treatment-induced ADA detected only at one sampling time point during the treatment or follow-up observation period (excluding the last sampling time point, which will be considered persistent unless shown to be undetectable at a later time) or
- Treatment-induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period less than 16 weeks, and the subject's last sampling time point is ADA-negative.

Persistent ADA response:

- Treatment-induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive

samples (irrespective of any negative samples in between) are separated by a period of 16 weeks or longer or

- Treatment-induced ADA detected only at the last sampling time point of the study treatment period or at a sampling time point with less than 16 weeks before an ADA-negative last sample.

The subject level ADA prevalence, incidence, and positive ADA response being transient or persistent (if applicable) will be calculated as the number and the proportion (percent) of the study population during the study period by treatment and dose. Subject level IM parameters (as described above) will be listed by treatment and dose for all evaluable subjects, and also appropriately summarized (using descriptive statistics) as median, quartiles (25% and 75%), and range and/or presented graphically, if deemed appropriate, by treatment and dose at the discretion of the designated study pharmacokineticist and/or statistician.

3.4.5.3 Evaluation of IM Impact on PK, PD, and Safety

If deemed necessary, the impact of IM on PK, PD, and safety may be evaluated by stratifying PK, PD, and selected safety measures by subject IM status and summarized using typical descriptive statistics. Other stratifications (e.g., based on antibody titer, onset of ADA, etc.) of selected PK, efficacy and safety assessments may also be performed if deemed warranted at the discretion of the pharmacokineticist, medical monitor, and/or biostatistician.

3.5 Pharmacodynamic Analysis

The PD analysis will be conducted in the Full Analysis Set and Per Protocol Set. The change and percent change from baseline in TTR and RBP4 will be summarized.

For healthy volunteer cohorts, the data will also be compared between the ION-682884 treatment groups and placebo using one-way ANOVA (if data departs substantially from normality, the Wilcoxon Rank Sum test will be used).

Note to File

Date: 7 March 2022

To: ION-682884-CS1 Clinical Study Report

From: [redacted]

Re: ION-682884-CS1 Tables, Figures, and Listings

Upon further review of the draft CSR, it was discovered that the parameter ATPTLDN (Nominal Timepoint from Previous Dose) was incorrectly computed in the ADPC file used to generate tables, figures, and listings (TFLs) received from Parexel with time stamp of 07Oct2021. The ADPC file was corrected and all TFLs listed below were subsequently updated with a time stamp of 07Feb2022.

- Tables: 14.2.2.1 to 14.2.2.4, 14.3.5.3-1 to 14.3.5.3-7, 14.3.5.4-1, 14.3.5.4-2, 14.3.5.5-1, 14.3.5.5-2, 14.3.5.6-1 to 14.3.5.6-4, 14.3.5.7-1 to 14.3.5.7-4, 14.3.5.8-1, 14.3.5.8-2, 14.3.5.9-1, and 14.3.5.9-2
- Figures: 14.2.2.1-1 to 14.2.2.1-5, 14.2.2.2, 14.2.2.3-1, 14.2.2.3-2, and 14.2.2.4
- Listings: 16.2.5.2.1 to 16.2.5.2.4, 16.2.8.7.1, and 16.2.8.7.2

ATPTLDN only applies to the TFLs detailed below, while the content of all other TFLs listed above were unaffected by the ATPTLDN correction. Thus, only the TFLs listed below were included in the CSR with time stamp of 07Feb2022, while all other TFLs listed above were kept in the CSR with time stamp of 07Oct2021.

- Tables: 14.2.2.1, 14.3.5.4-1 and 14.3.5.4-2
- Figures: 14.2.2.1-1 to 14.2.2.1-5, and 14.2.2.2
- Listing: 16.2.5.2.1

See electronic signature and date attached at end of document

[redacted]

Version:	1
Version Date:	06 Mar 2022
Title:	

APPROVALS:

[redacted], 06-Mar-2022 16:49:29 GMT+0000