An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 420915 in Patients With Familial Amyloid Polyneuropathy (FAP)

NCT02175004

27 January 2022

ionispharma.com

2855 Gazelle Court
Carlsbad, CA 92010

(760) 931-9200

Official Title: An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy (FAP)

NCT Number: NCT02175004

Document Dates: Protocol Amendment Version 5: 13-May-2020

16.1.1 PROTOCOL AND PROTOCOL AMENDMENTS

ROW	UK	Brazil	France
Original – 19Dec2013	-	-	-
Amend 1 – 08May2015	Suppl 1 – 08May2015	Suppl 1 – 22Mar2016	-
Amend 2 – 10Aug2015	Suppl 2 – 04Nov2015	-	Suppl 1 – 07Jul2015
Amend 3 – 07Mar2016	Suppl 3 – 07Mar2016	-	Suppl 2 – 07Mar2016
Amend 4 – 13May2016	Suppl 4 – 13May2016	-	-
Amend 5 – 22Feb2017	Suppl 5 – 23Mar2017	-	-
Addendum 1 to Amend 5 – 13May2020			

IONIS PHARMACEUTICALS, INC.

ISIS 420915-CS3

An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy (FAP)

Addendum 1 to Protocol Amendment 5 – 13 May 2020

EudraCT No: 2013-004561-13

Trial Sponsor

Ionis Pharmaceuticals, Inc.
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Phone: +01 760 931 9200
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Key Sponsor Contact

[redacted] Ph.D
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2855 Gazelle Court
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ISIS 42091S-CS3

Addeadum 1 to Protoml Amendment *S*

E11draCT No: 2013-004561-13

Clinical Phase: 3

An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 420915 in Patients with Familial Amyloid Polyoeuropathy (FAP)

Sponsor

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[redacted]

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ADDENDUM SIGNATURE PAGE

Protocol Number:	ISIS 420915-CS3
Protocol Title:	An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy (FAP)
Addendum:	Addendum 1 to Protocol Amendment 5
Date:	13 May 2020

I hereby acknowledge that I have read and understand the attached addendum to the clinical protocol, entitled "An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy (FAP)" dated 13 May 2020, 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)

SUMMARY OF ADDENDUM

Protocol Number:	ISIS 420915-CS3
Protocol Title:	An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy (FAP)
Protocol Amendment:	5
Addendum Number:	1
Addendum Date:	13 May 2020

Due to the COVID-19 pandemic, patients participating in ISIS 420915-CS3 may be prevented from attending study visits at study centers because of the policies of the centers (or the institution in which they are located), governmental restrictions on movement, or a patient's desire to minimize risk of infection.

In ISIS 420915-CS3, visits to study centers are required only for the study visits in Week 24 and Week 52 of Treatment Years 2, 3, 4, and 5 (all current study participants have progressed past Year 1). Therefore, the Sponsor issued guidance, on 17 March 2020, to the study centers with patients actively participating in ISIS 420915-CS3 that the Week 24 and Week 52 visits may be conducted remotely. The memorandum is attached as Appendix A.

Briefly, when patients do not attend on-site Week 26 or Week 52 visits, telephone contact between site staff and patients is required to collect adverse event and concomitant medication usage information and to assess the patients' general well-being. Collection of specimens for serum chemistry, hematology, and urinalysis is also required. Where possible, collection of specimens for the other laboratory tests specified for the visit are also to be collected.

APPENDIX A. MEMORANDUM TO STUDY INVESTIGATORS AND SITE PERSONNEL

MEMORANDUM

To:	Tegsedi ISIS 420915-CS3 ARG and BRA Study Investigators and Site Personnel
From:	Ionis Clinical Management Team
RE:	Study Modifications due to Coronavirus or COVID-19
Date:	17 MAR 2020

Given the rapid spread of the Coronavirus, or COVID-19, it is critical that we do our best to mitigate the impact of this outbreak, prevent illness, and ensure patient safety while patients are participating in ISIS 420915-CS3.

Ionis understands the need for flexibility and modifications during this time of heightened COVID-19 risk. For the next month, and continuing on a month by month basis:

- All study visits including the semi-annual visits required to be on-site (Wk 26 and 52) by the protocol may be conducted remotely.
- In place of the semi-annual required on-site visits (Wk 26 and 52),
    - We require a telephone contact with the patient(s) to collect AE(s) and conmed usage information and to assess the patient's general well-being.
    - We require collection of specimens for serum chemistry, hematology, and urinalysis.
    - Where possible, we ask for collection of specimens for the other laboratory tests [thyroid panel, the coagulation panel (PT, aPTT, INR), retinol, hs-CRP, PD panel, NT-proBNP, immunogenicity, and trough PK] if specified by protocol.
- For the Wk 13 and 39 visits and all of the Additional Visits, the protocol specified collections should be performed.
- Should a patient report any symptoms that are concerning, the PI can triage the patient accordingly.
- Protocol Deviations will need to be entered for any efficacy measure not performed due to the COVID-19 outbreak.

Ionis will continue to assess these modifications and will update this guidance on a monthly basis as we monitor the COVID-19 outbreak. Please escalate any concerns to the Clinical Study Management Team, as we continue to stay in operation.

ionispharma.com

2855 Gazelle Court
Carlsbad, CA 92010

(760) 931-9200

From: [redacted]
Sent: Tuesday, March 17, 2020 11:58 AM
To: [redacted] - Centro de Pesquisa Clfnica (Lar Escola);
Cc: [redacted] - Centro de Pesquisa Clinica (Lar Escola) (Contractor); [redacted] (Contractor); [redacted] (Contractor); [redacted]
Subject: Ionis CS3 COVID-19 memo
Attachments: TTR-CS3-COVID-19 Memo_17_Mar_2020.pdf

Importance: High

1111

Dear Dr.• , Dr,_ and Dr.• ,

Please see the attached memo from Ionis regarding the recent corona virus outbreak and instructions regarding the CS3 study and future patient visits.

Thank you and please revert with any questions or concerns.

Kind Regards,

[redacted] MPH, RN
[redacted]
ICON Clinical Research
External Tel: [redacted]
Mobile: [redacted]
Fax: [redacted]
Email: [redacted]

From: [redacted]
Sent: Tuesday, March 17, 2020 1:43 PM
To: [redacted]
Cc: [redacted] (Contractor)
Subject: FW: Ionis CS3 COVID-19 memo
Attachments: TTR-CS3-COVID-19 Memo_17_Mar_2020.pdf

Importance: High

Hi Dr. [redacted],

So sorry I forgot to add you to the email I just sent to LATAM sites, see attached please.

Regards,
[redacted]

From: [redacted]
Sent: Tuesday, March 17, 2020 2:58 PM
To: [redacted] - Centro de Pesquisa Clínica (Lar Escola)' [redacted] - Centro de Pesquisa Clínica (Lar Escola)' [redacted]
Cc: [redacted] (Contractor) [redacted] (Contractor) [redacted] (Contractor) [redacted]
[redacted] VID-19 memo

Importance: High

Dear Dr.• , Dr,_ and Dr.• ,

Please see the attached memo from Ionis regarding the recent corona virus outbreak and instructions regarding the CS3 study and future patient visits.

Thank you and please revert with any questions or concerns.

Kind Regards,

[redacted] MPH, RN
[redacted]
ICON Clinical Research
External Tel: [redacted]
Mobile: [redacted]
Fax: [redacted]
Email: [redacted]

IONIS PHARMACEUTICALS, INC.

ISIS 420915-CS3

An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy (FAP)

Protocol Supplement 5 - UK – 23 March 2017

EudraCT No: 2013-004561-13

Sponsor:

Ionis Pharmaceuticals, Inc.

2855 Gazelle Court

Carlsbad, CA 92010

ISIS 420915-CS3

An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy (FAP)

Protocol Supplement S - UK- 23 March 2017

Sponsor:

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[redacted]
MBBS, FRCP, FFPM, MBA

Protocol Supplement Signature Page

Protocol Number:	ISIS 420915-CS3
Protocol Title:	An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy (FAP)
Supplement:	5 - UK
Date:	23 March 2017

I hereby acknowledge that I have read and understand the attached clinical protocol supplement (Supplement 5 – UK), dated 23 March 2017, for the protocol entitled "An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy (FAP)", and agree to conduct the study as described herein.

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

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

Investigator's Signature

Investigator's Name *(please print)*

Date (DD Month YYYY)

Protocol Supplement - UK

Protocol Number:	ISIS 420915-CS3
Protocol Title:	An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy (FAP)
Supplement Number:	5 - UK
Date:	23 March 2017

The purpose of this supplement (to the global study protocol) is to fulfill MHRA requirements. The following changes will be made to the protocol:

1. The term "abstinence" will be further defined as "true abstinence" i.e., when this is in line with the preferred and usual lifestyle of the subject. 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."

The following table provides a summary list of the modifications to the protocol.

List of Protocol Modifications

Section	Modification	Rationale
Protocol Synopsis; Section 5.1 Inclusion Criteria #3 a and b	**Was:** 3. Satisfy one of the following: a Females: Non-pregnant and non-lactating; surgically sterile, postmenopausal, abstinent, or if engaged in sexual relations of childbearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 3 months after the last dose of ISIS 420915. b. Males: Surgically sterile, abstinent, or if engaged in sexual relations with a female of childbearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) during and for 3 months after the last dose of ISIS 420915.	The definition of abstinence as "true abstinence" is needed per the long duration of the clinical trial.

List of Protocol Modifications *Continued*

Section	Modification	Rationale
	Is: 3. Satisfy 1 of the following: a. Females: Non-pregnant and non-lactating; surgically sterile, postmenopausal, abstinent*, or if engaged in sexual relations of childbearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 3 months after the last dose of ISIS 420915. b. Males: Surgically sterile, abstinent*, or if engaged in sexual relations with a female of childbearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) during and for 3 months after the last dose of ISIS 420915. *Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the subject. 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."	

IONIS PHARMACEUTICALS, INC.

ISIS 420915-CS3

An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy (FAP)

Protocol Amendment 5 – 22 Feburary 2017

EudraCT No: 2013-004561-13

Sponsor:

Ionis Pharmaceuticals, Inc.

2855 Gazelle Court

Carlsbad, CA 92010

ISIS 420915-CSJ

An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy (FAP)

Protocol Amendment 5 - 22 Feburary 2017

Protocol History:

Original Protocol:	19 December 2013
Protocol Amendment I:	8 May 2015
Protocol Amendment 2:	10 August 2015
Protocol Amendment 3:	7 March 2016
Protocol Amendment 4:	13 May 2016

Sponsor:

Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 920I0

[redacted]
MD, MBA

ISIS 420915

Ionis Protocol Number ISIS 420915-CS3

Protocol Amendment 5

EudraCT No: 2013-004561-13

Clinical Phase: 3

An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy (FAP)

Trial Sponsor:
Ionis Phaimaceuticals, Inc.
2855 Gazelle Court
Cai·lsbad, CA 92010
Phone: +01 760 931 9200
Fax: +01 760 603 2700

Key Sponsor Contact:
[redacted] Ph.D.
[redacted]
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Phone: +01 760 603 2700

Date: 22 Feburaiy 2017

Confidentiality Statement

Protocol Signature Page

Protocol Number: ISIS 420915-CS3

Protocol Title: An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy (FAP)

Amendment: Amendment 5

Date: 22 Feburary 2017

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy (FAP)", dated 22 Feburary 2017, and agree to conduct the study as described herein.

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

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

Investigator's Signature

Investigator's Name *(please print)*

Date (DD Month YYYY)

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PROTOCOL AMENDMENT

Protocol Number: ISIS 420915-CS3

Protocol Title: An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy (FAP)

Amendment Number: 5

Amendment Date: 22 Feburary 2017

The main purpose of this amendment is to provide the opportunity for patients to receive a fourth and fifth year of treatment with a modified assessment schedule if at the end of 3 years of treatment ISIS 420915 is not commercially available in the country of the patient.

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

The following table provides a summary list of major changes to the protocol; added text in underlined bold, deleted text in strikethrough:

Protocol Section	Description of Change	Rationale
Synopsis 3.1 Study Design 3.4.3 Post-Treatment	**If at the end of 3 years of treatment, ISIS 420915 is not commercially available in the country of the patient, the patient may continue to receive treatment in this study for up to 2 years more or until ISIS 420915 becomes commercially available in the patient's country, whichever occurs earlier. At the end of the 5 years of treatment with ISIS 420915 in this study, if ISIS 420915 is not commercially available, patients may be allowed to continue receiving treatment with ISIS 420915 via an early access route to be defined by the Sponsor and depending on local regulations.** After completing the treatment period, patients will enter the 3-month post-treatment evaluation period. **If a patient discontinues treatment in this study, but is continuing to receive treatment with ISIS 420915 via another mechanism, the entry of the patient into the 3-month post-treatment evaluation period may be omitted.** ~~Alternatively, after completing the 3 year treatment period (Week 156 visit), a patient may be offered the opportunity to continue to receive ISIS~~	To provide the opportunity for patients to receive a fourth and fifth year of treatment if at the end of 3 years of treatment, ISIS 420915 is not commercially available in the country of the patient.

Protocol Section	Description of Change	Rationale
Synopsis 3.1 Study Design 3.4.3 Post-Treatment *Continued*	~~420915. Continuation of ISIS 420915 may occur via early access, a separate open label extension protocol, or other programs depending on local regulations. Patients may continue to receive treatment via 1 of these mechanisms until ONE (1) of the following is met:~~ • ~~ISIS 420915 is commercially available in the local country; or~~ • ~~ISIS 420915 is rejected by the regulatory authority in the local country, or~~ ~~Sponsor terminates access to ISIS 420915 for reasons including, but not limited to safety issues or emergent data~~	
Synopsis Study Design and Treatment Schema 3.4.3 Post-Treatment 6.1.3 Post-Treatment Period	**If a patient discontinues treatment in this study, but will continue to receive treatment with ISIS 420915 via another mechanism, the entry of the patient into the 3-month post-treatment evaluation period may be omitted.**	To avoid interruptions in therapy.
Synopsis Study Design and Treatment Schema 2.4 Rationale for Dose and Schedule of Administration 3.4 Overall Study Duration and Follow-up 3.4.2 Treatment 8.1 Study Drug Administration Appendix A Appendix C	Treatment period up to **5 years (Week 1 up to Y5-W52**)	To provide the opportunity for patients to receive a fourth and fifth year of treatment if at the end of 3 years of treatment, ISIS 420915 is not available in the country of the patient.
Study Design and Treatment Schema Appendix A Appendix C	**Post-treatment evaluation period is 3 months from last dose**	To provide flexibility, applicable to early terminations as well as completing Year 3 or Year 5 of treatment.
Synopsis 3.4.2 Treatment 6.1.2 Treatment Period	During the treatment period patients will report to the Study Center for evaluation and tests ~~9~~**5 times in year 1 (Weeks 1, 7, 13, 26, 52), and 2 times in each subsequent year (26th and 52nd week of each year).**	Language modified to provide generic description for Years 2-5.

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Protocol Section	Description of Change	Rationale
Synopsis 6.1.2 Treatment Period	There are ~~12~~**8 non-clinic visits (Weeks 4, 10, 15, 18, 21, 23, 29, 39) in Year 1 and 2 in each subsequent year (13th and 39th week of each year),** where labs will be collected by the Sponsor-appointed home healthcare service or the Study Center as arranged by the Study Center personnel or by local laboratory with prior Sponsor approval.	Language modified to provide generic description for Years 2-5.
6.1.2 Treatment Period Appendix A	The mNIS+7 assessment ~~and Norfolk QOL DN questionnaire are~~ will be conducted at Weeks 26, 52, 78, 104, 130, and 156. **The NIS assessment is conducted at Y4-W52 and Y5-W52. The Norfolk QOL-DN questionnaire is conducted at Weeks 26, 52, 78, 104, 130, and 156 as well as Y4-W52 and Y5-W52.**	Language modified to provide generic description for Years 2-5.
6.1.2 Treatment Period 8.5.3 Safety Monitoring Rules for Ocular Effects	During the treatment period, an ophthalmology examination will be performed at Weeks 26, 52, 78, 104, 130, 156 **and 2 times in each subsequent year (26th and 52nd week of each year).**	Language modified to provide generic description for Years 2-5.
8.9 Withdrawal of Patients from the Study	Other reasons for withdrawal of patients from the study might include: • At the discretion of the Investigator **or Sponsor** for medical reasons • At the discretion of the Investigator or Sponsor for noncompliance • Significant protocol deviation • Administrative decision by the Investigator or Sponsor • **ISIS 420915 becomes commercially available in the local country (patients in Year 4 or Year 5)** • **ISIS 420915 is rejected by the regulatory authority in the local country**	Language modified to include alternative reasons for withdrawal.
10.1.2 Efficacy Endpoints	• **Change in the NIS score and components from baseline to Y5-W52 and Y4-W52** • Change in the Norfolk QOL-DN questionnaire scores from baseline to Week 78 and Week 156 **and at the end of each subsequent treatment year (52nd week of each year)** • Change in PND score from baseline to Week 78 and Week 156 **and at the end of each subsequent treatment year (52nd week of each year)** • Change in GLS by ECHO from baseline to Week 78 and Week 156 **and at the end of each subsequent treatment year (52nd week of each year)** in the ISIS 420915-CS2 ECHO subgroup and in the Cardiomyopathy-ECHO (CM-ECHO) Set	Language modified to provide generic description for Years 2-5 and to reflect the change of NIS score as an efficacy measure in the study

Protocol Section	Description of Change	Rationale
10.1.3 Pharmacodynamic Endpoints 10.6.5 Pharmacodynamic Analysis	• Change from baseline in TTR level to Week 78 and Week 156 **and at the end of each subsequent treatment year (52nd week of each year)** • Change from baseline in RBP4 level to Week 78 and Week 156 **and at the end of each subsequent treatment year (52nd week of each year)**	Language modified to provide generic description for Years 2-5.
10.1.5 Exploratory Efficacy Endpoints	• Change in the ECHO parameters (except GLS) in the ISIS 420915-CS2 ECHO subgroup and in the Cardiomyopathy-ECHO (CM-ECHO) Set from baseline to Week 78 and Week 156 **and at the end of each subsequent treatment year (52nd week of each year)** • Change in NT-proBNP from baseline to Week 78 and Week 156 **and at the end of each subsequent treatment year and at the end of each subsequent treatment year (52nd week of each year)** • Change in the SF-36 questionnaire scores from baseline to Week 78 and Week 156 **and at the end of each subsequent treatment year (52nd week of each year)**	Language modified to provide generic description for Years 2-5.
10.3 Populations	The CM-ECHO set will include the subset of the ~~safety set that has~~ **420915-CS2 Randomized Set that had a diagnosis of TTR cardiomyopathy** at l~~east 1 evaluable post baseline~~ **study entry of the parent study, but are not in the ECHO Subgroup in the parent study, plus patients who qualified to participate in the ECHO Subgroup (whether consented or not). Patients who did not meet the criteria for the** ECHO ~~assessment and~~ **Subgroup or the CM-ECHO Set in ISIS 420915-CS2, but who are found to meet those criteria upon entry into ISIS 420915-CS3, may also be included in additional analysis** ~~will include patients that participated in the ISIS 420915-CS2 ECHO subgroup plus those patients that did not participate in the ECHO subgroup but who had a diagnosis of TTR cardiomyopathy at ISIS 420915-CS2 study entry. Patients who did not meet criteria for the ECHO Subgroup or the CM-ECHO Set in ISIS 420915-CS2, but who are found to meet those criteria upon entry into ISIS 420915-CS3, may also be included in additional analyses~~ (details will be found in the SAP).	Updated language to be consistent with SAP.

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Protocol Section	Description of Change	Rationale
10.4 Definition of Baseline	For safety, baseline for patients on active treatment in the parent study will be the parent study baseline. For patients on placebo in the parent study, baseline for safety will be **the last non-missing assessment prior to the first dose of ISIS 420915 in this study (Study Day 1) (details will be found in the SAP)**. ~~The Day 1 pre-dose value in this study~~ For efficacy, 2 baselines are defined for each patient: the parent study baseline and the baseline assessment in this study **(details will be found in the SAP)**. ~~The baseline for this study is defined as the End of Treatment assessment in the parent study (EOT Week 66 assessment).~~ Further details of which assessments will be considered baseline for Echo analyses for this study will be included in the SAP. **The baselines for additional analyses can be found in the SAP.**	Updated language to be consistent with SAP.
Synopsis 10.6.3 Efficacy Analysis	Change from baseline to Week 78 and Week 156 **and at Week 52 of each subsequent treatment year** will be summarized by treatment group of the parent study for the following efficacy measures: mNIS+7 score; **NIS score**; Norfolk QOL DN (total score, symptoms domain score for Stage 1 patients, and physical functioning/large fiber neuropathy domain score for Stage 2 patients); mBMI and BMI; components of the mNIS+7 (NIS, heat-pain sensory, touch-pressure sensory, nerve conduction and heart rate to deep breathing tests); and PND score; and the following exploratory measures: ECHO parameters, NT-proBNP, and SF-36 questionnaire.	To reflect the change of NIS score as an efficacy measure in the study.
Appendix A Appendix C	Added schedule for Year 4 and Year 5 • Visit Window was increased to +/- 14 days aside from early termination visit • ERG exam is not performed • Body Weight (fasting) is not performed • Immunogenicity is only performed once a year • PK trough is performed 3 times a year • Transthoracic ECHO is not performed and is not performed at the early termination visit if early termination is from Year 4-5 treatment • NIS is substituted for mNIS+7 and performed once per year • NIS is performed if early termination is from Year 4-5 treatment instead of mNIS+7 • Norfolk QOL-DN, SF-36 Questionnaire, and PND Score are performed once per year	Maintain safety schedule, simplify efficacy schedule.

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PROTOCOL SYNOPSIS

Protocol Title	An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy (FAP)
Study Phase	3
Indication	Familial Amyloid Polyneuropathy
Primary Objective	To evaluate the safety and tolerability of extended dosing with ISIS 420915 in patients with Familial Amyloid Polyneuropathy
Secondary Objectives	To evaluate the efficacy of extended dosing with ISIS 420915, based on change from baseline and progression rates, if applicable, in the following measures: • Modified Neuropathy Impairment Score +7 (mNIS+7) • Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) questionnaire: o total score (all patients) o symptoms domain score (Stage 1 patients) o physical functioning/large fiber neuropathy domain score (Stage 2 patients) • Modified body mass index (mBMI) and body mass index (BMI) • NIS, heat-pain sensory, touch-pressure sensory, nerve conduction and heart rate to deep breathing tests (components of mNIS+7) • Polyneuropathy disability score (PND) • Global longitudinal strain (GLS) by echocardiogram (ECHO) in the ISIS 420915-CS2 ECHO subgroup and in the Cardiomyopathy-ECHO (CM-ECHO) Set To evaluate the pharmacodynamic (PD) effect of extended dosing with ISIS 420915 based on change from baseline in transthyretin (TTR) and retinol binding protein 4 (RBP4) To evaluate the plasma trough levels of ISIS 420915
Exploratory Objective(s)	To evaluate the change from baseline in the following measures: • ECHO parameters (except GLS) in the ISIS 420915-CS2 ECHO subgroup and in the Cardiomyopathy-ECHO (CM-ECHO) Set • Plasma N-terminal prohormone of brain natriuretic peptide (NT-proBNP) • SF-36 questionnaire
Study Design	This is a multicenter open-label study. Eligible patients who have satisfactorily completed ISIS 420915-CS2 will receive 300 mg ISIS 420915 once weekly for 156 weeks (3 years). Patients will also receive supplemental doses of the recommended daily allowance of vitamin A. If at the end of 3 years of treatment, ISIS 420915 is not commercially available in the country of the patient, the patient may continue to receive treatment in this study for up to 2 years more or until ISIS 420915 becomes commercially available in the patient's country, whichever occurs earlier. At the end of the 5 years of treatment with ISIS 420915 in this study, if ISIS 420915 is not commercially available, patients may be allowed to continue receiving treatment with ISIS 420915 via an early access route to be defined by the Sponsor and depending on local regulations. After completing the treatment period, patients will enter the 3-month post-treatment evaluation period. If a patient discontinues treatment in this study, but is continuing to receive treatment with ISIS 420915 via another mechanism, the entry of the patient into the 3-month post-treatment evaluation period may be omitted.
Number of Patients	Approximately 135 patients may be eligible to enroll in this study

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PROTOCOL SYNOPSIS *Continued*

Study Population	Inclusion Criteria: 1. Completion of ISIS 420915-CS2 treatment with the following as judged by the Investigator and Sponsor: a. Satisfactory completion of dosing and EOT efficacy assessments b. No significant tolerability issues c. Satisfactory compliance to the ISIS 420915-CS2 protocol requirements Under special circumstances, patients that participated in ISIS 420915-CS2 but did not complete the full treatment period may be allowed to participate in this study with approval from the Sponsor. 2. Willingness to take vitamin A supplement 3. Satisfy 1 of the following: a. Females: non-pregnant and non-lactating; surgically sterile, postmenopausal, abstinent, or if engaged in sexual relations of childbearing potential, patient is using an acceptable contraceptive method from the time of signing the informed consent form until at least 3 months after the last dose of ISIS 420915 b. Males: Surgically sterile, abstinent, or if engaged in sexual relations with a female of childbearing potential, patient is utilizing an acceptable contraceptive method during and for 3 months after the last dose of ISIS 420915 4. Must have given written informed consent (signed and dated) and any authorization required by local law and be able to comply with all study requirements Exclusion Criteria: 1. Have any new condition or worsening of existing condition that in the opinion of the Investigator or Sponsor would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study
Treatment Groups	All patients will receive 300 mg ISIS 420915 given once weekly. However, patients that had a dose reduction or schedule change in ISIS 420915-CS2 may continue with the same dose or schedule in this study.
Study Drug Dosage and Administration	ISIS 420915 will be administered as a weekly subcutaneous (SC) injection.
Rationale for Dose and Schedule Selection	This is the same dose and schedule used during Weeks 2 to 65 in the ISIS 420915-CS2 study.
Study Visit Schedule and Procedures	For an individual patient, a maximum period of 4 weeks is allowed between a patient's last dose in ISIS 420915-CS2 (CS2 Week 65 Visit) and initiation of dosing in this study (CS3 Day 1 visit). Periods longer than 4 weeks may be considered after discussion and approval by the Study Medical Monitor. However, the intention is to minimize the treatment pause between the two studies. Ideally, the first dose in this study should be administered 1-week after the last dose in ISIS 420915-CS2. The study for an individual patient will generally consist of the following periods: • A ≤ 4-week screening period • A 3 to 5-year treatment period during which ISIS 420915 will be administered as a once weekly SC injection • A 3-month post-treatment evaluation period

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PROTOCOL SYNOPSIS *Continued*

Study Visit Schedule and Procedures *Continued*	Screening Period: A period of ≤ 4 weeks is allowed to complete the screening procedures outlined in the schedule of procedures in Appendix A. Safety clinical laboratory parameters and assessments from the ISIS 420915-CS2 study may be used for screening evaluation provided that they were taken within 4 weeks of Day 1. Periods longer than 4 weeks may be considered after discussion and approval by the Study Medical Monitor. Treatment Period: During the treatment period patients will report to the Study Center for evaluation and tests 5 times in Year 1 (Weeks 1, 7, 13, 26, 52) and 2 times in each subsequent year (26th and 52nd week of each year). Physical examination, collection of blood for measurement of safety clinical laboratory parameters and specialty labs, measurement of vital signs, and collection of adverse events and concomitant medication/procedure information will be performed according to the schedule of procedures in Appendix A. The following assessments will also be performed at specified visits during the study: mNIS+7, NIS, Norfolk QOL-DN questionnaire, SF-36 questionnaire, PND score, body weight, ophthalmology examination, electroretinogram (ERG), electrocardiogram (ECG), and transthoracic ECHO examination. There are 8 non-clinic visits in Year 1 (Weeks 4, 10, 15, 18, 21, 23, 29, 39) and 2 in each subsequent year (13th and 39th week of each year) where labs will be collected by the Sponsor appointed home healthcare service or the Study Center as arranged by the Study Center personnel or by local laboratory with prior Sponsor approval. In addition, platelets will be collected weekly and serum creatinine every 2-3 weeks (Appendices A and C). Patients may also be contacted by phone to collect adverse events, concomitant medication and concomitant procedure information (Appendix A). Patients may be provided with prefilled syringes, when available in each country. Once available a patient preference questionnaire may be conducted. ISIS 420915 will be administered by either the Study Center personnel or at home by the patient/caregiver. In order to ensure maintenance of the study blind in ISIS 420915-CS2, TTR, RBP4, retinol, and NT-proBNP from the first 13 weeks of treatment in this study will not be available to the Sponsor, Investigators, Study Center Personnel, or the patients until the ISIS 420915-CS2 study is unblinded. Post-Treatment Evaluation Period: After discontinuation of treatment with ISIS 420915 patients will enter a 3-month post-treatment evaluation period as outlined in the Schedule of Procedures in Appendix A and C. If a patient discontinues treatment in this study, but is continuing to receive treatment with ISIS 420915 via another mechanism, the entry of the patient into the 3-month post-treatment evaluation period may be omitted.

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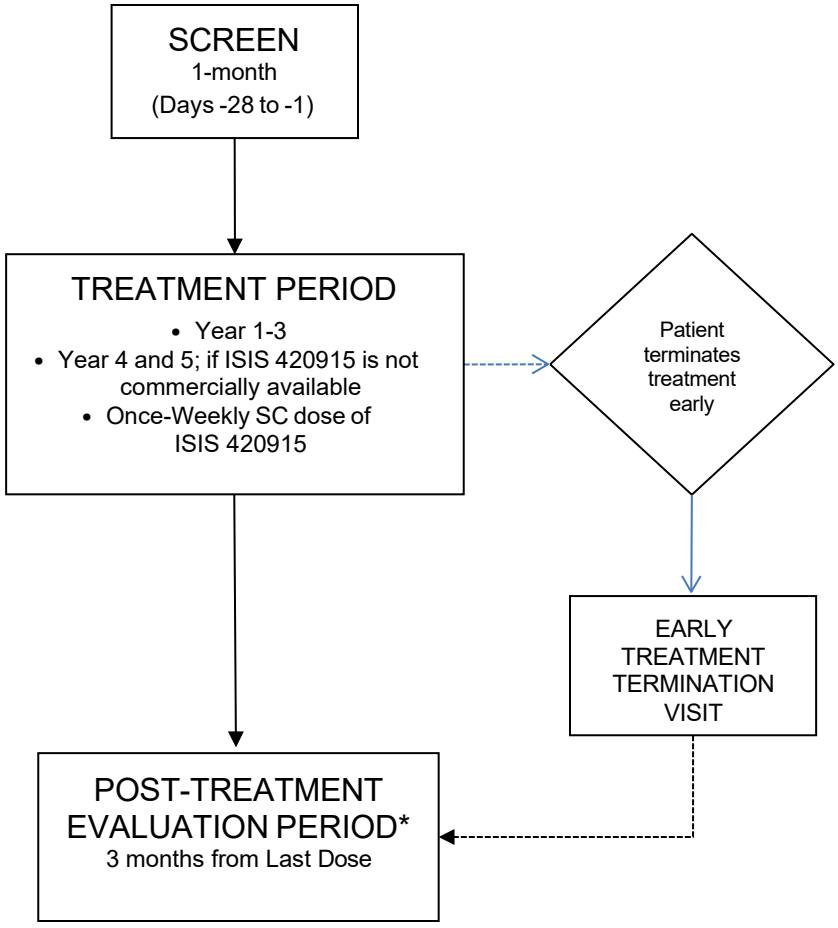
PROTOCOL SYNOPSIS *Continued*

Safety and Tolerability Evaluations	The safety and tolerability of ISIS 420915 will be assessed on an ongoing basis by the Study Medical Monitor and by the Independent Data and Safety Monitoring Board (DSMB), as outlined in the Safety Management Plan and DSMB Charter. Safety and tolerability assessments include: adverse events, vital signs, physical examination, clinical laboratory tests, 12 lead ECG, use of concomitant medications, ophthalmology examination, and ERG examination.
Efficacy Evaluations	Efficacy evaluations include change from baseline and progression rates, if applicable, in mNIS+7, NIS, Norfolk QOL-DN questionnaire scores, mBMI/BMI, PND, ECHO parameters, and NT-proBNP.
Pharmacokinetic Evaluations	Plasma samples will be taken for measurement of ISIS 420915 trough and post-distribution levels at the time points detailed in Appendix A.
Pharmacodynamic Evaluations	Circulating levels of TTR and RBP4 will be determined throughout the study as detailed in Appendix A.
Statistical Considerations	No sample size calculations were performed as this is an extension study to the double-blind placebo controlled ISIS 420915-CS2 study.

STUDY DESIGN AND TREATMENT SCHEMA



* The post-treatment evaluation period may be omitted if the patient discontinues treatment in this study, but continues to receive treatment with ISIS 420915 via another mechanism

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STUDY GLOSSARY

Abbreviation/Acronym	Definition
ACE	angiotensin-converting enzyme
Alb/C ratio	Albumin/Creatinine ratio (performed on urine sample)
aPTT	activated partial thromboplastin time
ARB	angiotensin II receptor blockers
ASO	antisense oligonucleotide
BMI	body mass index
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
DSMB	Data and safety monitoring board
ECG	electrocardiogram
ECHO	echocardiogram
EOT	End-of-Treatment
ERG	electroretinogram
ET	Early termination
FAC	Familial amyloid cardiomyopathy
FAP	Familial amyloid polyneuropathy
GLS	Global longitudinal strain
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LLN	lower limit of normal
mBMI	Modified body mass index (requires determination of plasma albumin levels; mBMI = BMI x serum albumin g/L)
MMRM	Mixed Effects Model with Repeated Measures
mNIS+7	Modified neuropathy impairment score +7. Standard NIS but with modifications made to the +7 component
MOE	2′-*O*-(2-methoxyethyl)
NIS	Neuropathy impairment score
Non-clinic visit	Patients can choose to have these visits via the Sponsor appointed home healthcare service or at the Study Center. In addition, local laboratory can be used with Sponsor approval.
Norfolk QOL-DN	Norfolk quality of life-diabetic neuropathy questionnaire

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Abbreviation/Acronym	**Definition**
NSAID	nonsteroidal anti-inflammatory drugs
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
OLE	Open label extension
P/C ratio	Protein/Creatinine ratio (performed on urine sample)
PD	pharmacodynamic
PK	pharmacokinetic
PND Score	Polyneuropathy disability score
RDA	Recommended daily allowance
RBP4	Retinol binding protein 4
SAE	serious adverse event
SC	subcutaneous
Study Day 1	Defined as the first day ISIS 420915 is administered to the patient
Study Drug	ISIS 420915
SUSARs	suspected unexpected serious adverse reactions
TTR	Transthyretin
TUCA	Tauroursodeoxycholic acid
ULN	Upper limit of normal
UTR	Untranslated region

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1. OBJECTIVES

1.1 Primary Objective

To evaluate the safety and tolerability of extended dosing with ISIS 420915 in patients with Familial Amyloid Polyneuropathy.

1.2 Secondary Objectives

To evaluate the efficacy of extended dosing with ISIS 420915 based on change from baseline and progression rate, if applicable, in the following measures:

- Modified Neuropathy Impairment Score +7 (mNIS+7)
- Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) questionnaire:
    - total score (all patients)
    - symptoms domain score (Stage 1 patients)
    - physical functioning/large fiber neuropathy domain score (Stage 2 patients)
- Modified body mass index (mBMI) and body mass index (BMI)
- NIS, heat-pain sensory, touch-pressure sensory, nerve conduction, and heart rate to deep breathing tests (components of mNIS+7)
- Polyneuropathy disability score (PND score)
- To evaluate the pharmacodynamic (PD) effect of extended dosing with ISIS 420915 based on change from baseline in transthyretin (TTR) and retinol binding protein 4 (RBP4)
- Global longitudinal strain (GLS) by echocardiogram (ECHO) in the ISIS 420915-CS2 ECHO subgroup and in the Cardiomyopathy-ECHO (CM-ECHO) Set

To evaluate the plasma trough levels of ISIS 420915.

1.3 Exploratory Objectives

To evaluate the change from baseline in the following measures:

- ECHO parameters (except GLS) in the ISIS 420915-CS2 ECHO subgroup and in the Cardiomyopathy-ECHO (CM-ECHO) Set
- Plasma N-terminal prohormone of brain natriuretic peptide (NT-proBNP)
- SF-36 questionnaire

2. BACKGROUND AND RATIONALE

2.1 Overview of Disease

Transthyretin is synthesized primarily in the liver and is secreted 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 an association with RBP4. Transthyretin amyloidosis is a rare hereditary disease caused by mutations in the TTR protein. The disease causing mutations destabilize the normal tetrameric structure of TTR causing its dissociation into free monomers and subsequent aggregation into insoluble fibril deposits. These deposits are found in multiple organs including the peripheral nervous system, gastrointestinal tract and heart. They result in local damage to cells leading to a peripheral polyneuropathy (called Familial Amyloid Polyneuropathy or FAP) and a cardiomyopathy (called Familial Amyloid Cardiomyopathy or FAC). FAP can be classified into 3 stages of disease based on ambulatory status: Stage 1 – do not require assistance with ambulation; Stage 2 – require assistance with ambulation; Stage 3 – wheelchair bound (Coutinho et al. 1980). The total worldwide prevalence of FAP has been estimated at approximately 10,000 patients (Coelho et al. 2008).

2.2 Therapeutic Rationale

ISIS 420915 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 FAP patients with ISIS 420915 is to reduce the levels of mutated and wild-type TTR protein secreted by the liver. It should be noted that antisense oligonucleotides (ASOs) are highly charged hydrophilic molecules that do not cross the blood brain barrier (Levin et al. 2008) and thus systemic treatment with ISIS 420915 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 ISIS 420915 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 orthotopic liver transplantation, with the exception that ISIS 420915 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.

There is a high unmet medical need for both Stage 1 and Stage 2 FAP patients worldwide. For Stage 2 patients, there is currently no approved therapy and these patients are often not candidates for liver transplant due to advanced age, health reasons, or cardiac involvement. For Stage 1 patients, Vyndaqel® is currently the only approved therapy. However, it is only approved in some countries and is not yet widely reimbursed or established as the standard of care.

2.3 ISIS 420915

2.3.1 Mechanism of Action

ISIS 420915 is a second-generation ASO drug targeted to transthyretin. It is complementary to a region within the 3′ untranslated region (3′ UTR) of the transthyretin mRNA and binds to the mRNA by Watson and Crick base pairing. The hybridization (binding) of ISIS 420915 to the cognate mRNA results in the RNase H-mediated degradation of the transthyretin mRNA, thus

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preventing production of the transthyretin protein. Maximal antisense-mediated reduction of target mRNA levels is typically greater than 90% of contrnl levels in sensitive tissues (Crooke and Bennett 1996; Zhang et al. 2010). Furthe1more, reduction in target mRNA levels using this approach correlates directly with a subsequent reduction in target protein levels.

2.3.2 Chemistry

Chemically, ISIS 420915 is a synthetic oligomer of 20 nucleotides (i.e., a 20-mer) that are connected sequentially by phosphorothioate linkages. The nucleotide sequence of ISIS 420915 (Figure 1) is complementaiy to a 20-nucleotide stretch within the 3' UTR region of the transthyretin protein mRNA. Strncturally, the oligonucleotide has 3 regions. Two (2) of them, the 5 nucleotides at the 5' end and the 5 nucleotides at the 3' end, ai·e composed of 2'-0-(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) ainelioration of some of the high dose toxicities thereby resulting in an improved safety profile compai·ed to first generation antisense diugs containing phosphorothioate modified oligodeoxynucleotides (DNA) (Henry et al. 2000). The third region, the central po1tion of the oligonucleotide, is composed of 10 oligodeoxynucleotides. This chimeric design is called a MOE-Gapmer, and ISIS 420915 employs this chimeric strncture to enable use of the RNase H-mechanism for antisense activity. This is because while the 2'-MOE modification confers increased stability and affinity, it does not suppo1t RNase H catalysis of RNA hybridized to 2'-MOE-modified nucleotides (McKay et al. 1999). This is caused by confonnational changes induced in the heteroduplex by 2'-alkoxy:RNA hybrids that are not recognized by RNase H enzymes (Inoue et al. 1987; Monia et al. 1993). By limiting the 2'-MOE modification to nucleotides flanking the phosphorothioate oligodeoxynucleotide core, the beneficial attributes of the 2'-MOE chemistry ai·e preserved while also retaining RNase H recognition.

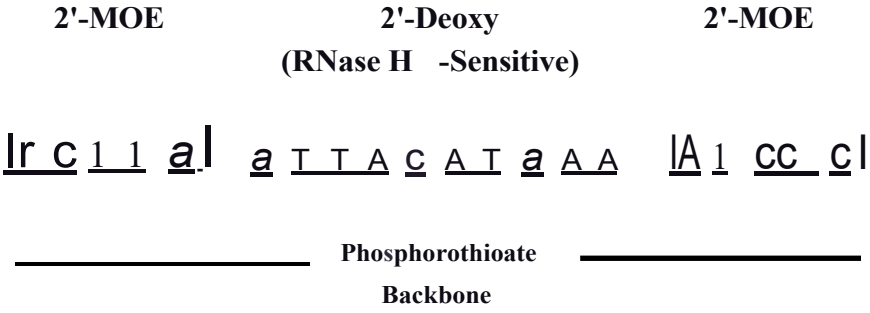

Figure 1 Design of Chimeric 2'-MOE Phosphorothioate Oligonucleotides (MOE-Gapmer). The sequence of ISIS 420915 is shown

2.3.3 Preclinical Experience

Detailed information concerning the preclinical studies conducted with ISIS 420915 can be found in the Investigator's Brochure. A summary is included below.

The nonclinical pharmacokinetics and toxicology evaluation of ISIS 420915 includes repeat dose studies up to 6 and 9 months in the CD-1 mouse and cynomolgus monkey, respectively. Nonclinical findings following ISIS 420915 treatment were, in general, non-specific class effects that are typical for 2′-MOE ASOs (Henry et al. 2008) and no findings were considered related to pharmacologic inhibition of TTR. Class effects occurred in a dose- and duration-dependent manner. In the monkey they included transient effects on acute complement activation (at doses ≥ 10 mg/kg/wk) and acute elevations in activated partial thromboplastin time (aPTT) (at doses ≥ 12 mg/kg/wk). The changes in aPTT were not cumulative over the course of the 9-month monkey study. In the mice, there was evidence of inflammation that included the presence of minimal to moderate mononuclear cell infiltrates in the sinusoids of liver, lymph nodes and the subcutaneous injection site at doses ≥ 40 mg/kg/wk after 3 and 6 months of treatment. Nonclinical pharmacokinetics (PK) of ISIS 420915 was similar to other second-generation ASOs. The exposure of ISIS 420915 in plasma and tissue was dose-dependent. The majority of ISIS 420915 was cleared from plasma within hours due mainly to distribution to tissues, with kidneys and liver having the highest concentrations. The half-life in kidney and liver was approximately 13.5 days and 18.8 days, respectively, consistent with the plasma terminal elimination half-life of 17.0 days (at 8 mg/kg) after 4 doses.

2.3.4 Clinical Experience

Two (2) clinical studies have been conducted with ISIS 420915; ISIS 420915-CS1 which is complete and ISIS 420915-CS2 which is ongoing. Detailed information concerning the ISIS 420915-CS1 and ISIS 420915-CS2 studies can be found in the Investigator's Brochure. A summary of each study is included below.

ISIS 420915-CS1 was a Phase 1 double-blind, placebo-controlled, dose escalation study designed to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of single and multiple doses of ISIS 420915 administered by subcutaneous injection to healthy subjects. The study enrolled 65 healthy volunteers (16 in the single dose cohorts and 49 in the multiple dose cohorts). Four (4) single dose levels (50, 100, 200, and 400 mg) and 5 multiple dose levels (50, 100, 200, 400 and 300 mg) were evaluated sequentially in the order listed. Subjects enrolled in the multiple-dose cohorts received a total of 6 doses of Study Drug administered by subcutaneous (SC) injection: 3 doses on alternate days during the first week (Days 1, 3, and 5) and then once a week for the next 3 weeks (Days 8, 15, and 22).

ISIS 420915 was well-tolerated at the dose levels and dose regimens tested in ISIS 420915-CS1. There were no serious adverse advents (SAEs). Two (2) discontinuations were considered possibly related to ISIS 420915 by the Sponsor, 1 due to constitutional symptoms (400 mg subject) and 1 due to injection site reactions (300 mg subject). The main safety findings included; 1) mild injection site reactions characterized most often by pain and erythema, 2) transient C-reactive protein elevations, primarily associated with the first injection and not associated with symptoms, and 3) retinol reductions below the lower limit of normal (LLN) which were asymptomatic and an expected consequence of transthyretin reduction.

Plasma transthyretin levels were evaluated in all cohorts and dose-dependent reductions were observed after both single and multiple-dose administration. In the multiple-dose cohorts, the mean percent reductions in transthyretin were -8%, -22%, -53%, -75% and -76% in the 50, 100, 200, 300, and 400 mg cohorts, respectively. The therapeutic goal for ISIS 420915 is to reduce transthyretin levels as much as possible at a dose level that will not cause unacceptable toxicity. Therefore, the 300 mg dose level which gave similar transthyretin reductions as the 400 mg dose level, was selected for the ISIS 420915-CS2 Phase 2/3 study.

ISIS 420915-CS2 is a Phase 2/3 multicenter, double-blind, placebo-controlled study to assess the efficacy and safety of ISIS 420915 in patients with FAP. The study plans to enroll approximately 135 patients randomized 2:1 (ISIS 420915 to placebo) to receive 300 mg ISIS 420915 or placebo. The Study Drug is administered 3 times during the Week 1 and once weekly during Weeks 2 to 65.

2.4 Rationale for Dose and Schedule of Administration

The dose level and schedule in the present open label extension (OLE) study (300 mg ISIS 420915 administered once weekly) is the same dose and schedule used during Weeks 2 to 65 in the preceding ISIS 420915-CS2 study. Antisense oligonucleotides of this class have been safely administered intravenously and subcutaneously in multiple clinical studies at doses up to 1000 mg (Kwoh 2008) and treatment duration's ≥ 6 months (Chi et al 2008; Raal et al. 2010) and > 24 months (Santos et al. 2012). The patients randomized to ISIS 420915 in ISIS 420915-CS2 receive 65 weeks (15 months) of treatment in that study followed by up to an additional 260 weeks (5 years) in the present OLE study. The safety and tolerability of the proposed 325-week dosing period is also supported by nonclinical chronic toxicology studies with ISIS 420915.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a multicenter open-label study. Eligible patients who have satisfactorily completed ISIS 420915-CS2 will receive 300 mg ISIS 420915 once weekly for 156 weeks (3 years). Exceptions will be given to patients that had a dose reduction or schedule change in ISIS 420915-CS2 who may continue with the same dose level or schedule in this study. All patients will receive supplemental doses of the recommended daily allowance (RDA) of vitamin A.

If at the end of 3 years of treatment, ISIS 420915 is not commercially available in the country of the patient, the patient may continue to receive treatment in this study for up to 2 years more or until ISIS 420915 becomes commercially available in the patient's country, whichever occurs earlier. At the end of the 5 years of treatment with ISIS 420915 in this study, if ISIS 420915 is not commercially available, patients may be allowed to continue receiving treatment with ISIS 420915 via an early access route to be defined by the sponsor and depending on local regulations. After completing the treatment period, patients will enter the 3-month post-treatment evaluation period. If a patient discontinues treatment in this study, but is continuing to receive treatment with ISIS 420915 via another mechanism, the entry of the patient into the 3-month post-treatment evaluation period may be omitted.

3.2 Number of Study Centers

This is a multicenter, worldwide study to be conducted at study centers that enroll patients in ISIS 420915-CS2.

3.3 Number of Patients

Approximately 135 patients may be eligible to enroll in this study.

3.4 Overall Study Duration and Follow-up

The study will consist of the following periods:

- A ≤ 4-week screening assessment period
- A treatment period of up to 260 weeks (Y5-W52)
- A 3-month post-treatment evaluation period

3.4.1 Screening Assessment

A maximum period of 4 weeks is allowed between a patient's last dose in ISIS 420915-CS2 (CS2 Week 65 visit) and initiation of dosing in this study (CS3 Day 1 visit). Periods longer than 4 weeks may be considered after discussion and approval by the Study Medical Monitor. However, the intention is to minimize the treatment pause between the 2 studies. Ideally the first dose in this study should be administered 1-week after the last dose in ISIS 420915-CS2.

3.4.2 Treatment

The treatment period is up to 260 weeks (5 years) in duration. ISIS 420915 will be administered as a once-weekly SC injection at the Study Center or at home by the patient or caregiver. Patients are to report to the Study Center for evaluations 5 times in Year 1 (Weeks 1, 7, 13, 26, 52) and 2 times in each subsequent year (26^{th} and 52^{nd} week of each year). There are also non-clinic visits including weekly platelet monitoring where patients will have blood collected by local laboratory, Sponsor appointed home healthcare service, or the Study Center.

3.4.3 Post-Treatment

After completion of treatment, patients will enter a 3-month post-treatment evaluation period that consists of clinic and non-clinic visits for safety monitoring.

If a patient discontinues treatment in this study, but is continuing to receive treatment with ISIS-420915 via another mechanism, the entry of the patient into the 3-month post-treatment evaluation period may be omitted.

3.5 End of Study

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

3.6 Data and Safety Monitoring Board

The independent Data and Safety Monitoring Board (DSMB) for ISIS 420915-CS2 will review the safety and tolerability of ISIS 420915 during this OLE study at a frequency and duration as outlined in the Safety Management Plan and DSMB Charter.

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4. PATIENT ENROLLMENT

4.1 Screening

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

Patients must sign the consent form before any screening tests or assessments are performed. At the time of consent, the patient will be considered enrolled into the study. Patients will maintain the same patient identification number that was assigned in ISIS 420915-CS2 throughout this OLE study.

4.2 Randomization

There is no randomization in this OLE study. All patients will receive ISIS 420915, including patients randomized to either ISIS 420915 or placebo in ISIS 420915-CS2.

4.3 Replacement of Patients

Patients who withdraw from the study will not be replaced.

5. PATIENT ELIGIBILITY

To be eligible to participate in this study candidates must meet the following eligibility criteria within 4 weeks of Study Day 1.

5.1 Inclusion Criteria

1. Completion of ISIS 420915-CS2 with the following as judged by the Investigator and Sponsor:

   a. Satisfactory completion of dosing and End-of-Treatment (EOT) efficacy assessments

   b. No significant tolerability issues

   c. Satisfactory compliance to the ISIS 420915-CS2 protocol requirements

   Under special circumstances, patients that participated in ISIS 420915-CS2 but did not complete the full treatment period may be allowed to participate in this study with approval from the Sponsor.

2. Willingness to take vitamin A supplements

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3. Satisfy 1 of the following:

   a. Females: Non-pregnant and non-lactating; surgically sterile, postmenopausal, abstinent, or if engaged in sexual relations of childbearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 3 months after the last dose of ISIS 420915.

   b. Males: Surgically sterile, abstinent, or if engaged in sexual relations with a female of childbearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) during and for 3 months after the last dose of ISIS 420915.

4. Must have given written informed consent (signed and dated) and any authorization required by local law and be able to comply with all study requirements

5.2 Exclusion Criteria

1. Have any new condition or worsening of existing condition that in the opinion of the Investigator or Sponsor would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study

6. STUDY PROCEDURES

6.1 Study Schedule

All required study procedures are outlined in Appendix A.

6.1.1 Screening Assessment Period

Before any study-specific procedures or evaluations are initiated, patients must sign and date the informed consent form. A maximum period of 4 weeks is allowed between a patient's last dose in ISIS 420915-CS2 (CS2 Week 65 visit) and initiation of dosing in this study (CS3 Day 1 visit). Periods longer than 4 weeks may be considered after discussion and approval by the Study Medical Monitor. All screening assessments must be completed during this period. An exception is the 24-hour urine collection (which includes a serum creatinine blood draw) that may be done at any time during the screening period or during Week 1 on treatment. Safety clinical laboratory parameters and assessments from ISIS 420915-CS2 may be used for screening evaluation if they were obtained within 4 weeks of Study Day 1. A longer period may be considered after discussion and approval from the Study Medical Monitor.

6.1.2 Treatment Period

Patients will report to the Study Center for evaluations and tests 5 times during Year 1 (Study Weeks 1, 7, 13, 26, 52) and 2 times in each subsequent year (26^{th} and 52^{nd} week of each year). Physical examination, collection of blood for measurement of safety clinical laboratory parameters and specialty labs, measurement of vital signs, and collection of adverse events and concomitant medication/procedure information will be performed according to the Schedule of Procedures in Appendix A. The following assessments will also be performed at specified visits during the study: mNIS+7, NIS, Norfolk QOL-DN questionnaire, SF-36 questionnaire, PND score, body weight, ophthalmology examination, electroretinogram (ERG), electrocardiogram (ECG), and transthoracic ECHO examination.

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Non-clinic visits will occur 8 times during Year 1 (Weeks 4, 10, 15, 18, 21, 23, 29, 39) and 2 times in each subsequent year (13th and 39th week of each year), where patients' labs will be collected by the Sponsor appointed home healthcare service, or the Study Center as arranged by the Study Center personnel or by local laboratory with prior Sponsor approval. In addition, platelets will be collected weekly and serum creatinine will be collected every 2-3 weeks (see Appendices A and C). Patients may also be contacted by phone to collect adverse events, concomitant medication, and concomitant procedure information.

ISIS 420915 can be administered once weekly by Study Center personnel or at home by the patient/caregiver. If ISIS 420915 is administered during a clinic or non-clinic visit, all blood samples should be drawn prior to administration. Ideally, blood draws should occur 7 days after the previous dose. Dosing instructions and training will be provided to the patient/caregiver where applicable. It is anticipated that the Study Drug configuration may change during the course of the study, from the configuration of stoppered glass vials to prefilled syringes (PFS). During this transition, patients may be requested to complete a short patient preference questionnaire.

Patients will also take daily oral supplemental doses of the RDA of vitamin A (approximately 3000 IU or closest approximate dose as available in the region where the patient resides). Vitamin A may be provided as either a single vitamin A supplement or as part of a multivitamin. The vitamin A supplement should be taken throughout the treatment and post-treatment evaluation periods.

To ensure maintenance of the study blind in the ongoing ISIS 420915-CS2 study, TTR, RBP4, retinol, and NT-proBNP from the first 13 weeks of treatment in this study will not be available to the Sponsor, Investigators, Study Center Personnel, or the patients until the ISIS 420915-CS2 study is unblinded.

The mNIS+7 assessment will be conducted at Weeks 26, 52, 78, 104, 130, and 156. The NIS assessment will be conducted at Y4-W52 and Y5-W52. The Norfolk QOL-DN questionnaire is conducted at Weeks 26, 52, 78, 104, 130, 156, and Y4-W52 and Y5-W52. The Norfolk QOL-DN questionnaire should be the first assessment performed at these visits. If ISIS 420915 administration, ERG, or ophthalmology examinations are to be performed on the same day as an mNIS+7 or NIS assessment, they should be performed after the mNIS+7 or NIS assessment is complete. For Week 78 and Week 156 visits, 2 mNIS+7 assessments will be performed on separate days. A maximum of 2 weeks from the visit (Week 78 or Week 156) will be allowed to complete both assessments.

For Weeks 4-52 there is a ± 7-day visit window. After Week 52 the visit window is ± 10-day. All reasonable attempts should be made to ensure compliance with the visit schedule as outlined in the schedule of procedures (Appendix A). However, if a visit does not occur or is delayed, all subsequent visits should be calculated based on the time elapsed since Day 1 rather than from the date of the previous visit.

The Study Day 1 ECHO can be done any time in the screening period or up to 2 weeks after Day 1. The Day 1 ECHO is not done if the Week 65 ECHO was conducted in ISIS 420915-CS2. A ± 2-week window is given for all other ECHOs.

During the treatment period, an ophthalmology examination will be performed at Weeks 26, 52, 78, 104, 130, 156, and 2 times in each subsequent year (26th and 52nd week of each year). An ERG examination will be performed at Weeks 78 and 156. A window of ± 2 weeks is allowed for these eye examinations. Early termination ERG and ophthalmology examinations are only done if the patient discontinues treatment after ≥ 9 months of dosing or unless deemed necessary by Investigator or Study Medical Monitor.

6.1.3 Post-Treatment Period

After discontinuation of treatment with ISIS 420915, patients will enter the 3-month post-treatment evaluation period. This period consists of clinic and non-clinic visits for safety monitoring as outlined in the Schedule of Procedures (Appendix A and C). Weekly platelet and every 2-3 week serum creatinine testing is required for a minimum of 6 weeks after the last dose of Study Drug (this includes early termination patients as well as patients that complete the full treatment period). Patients that terminate treatment early and do not withdraw consent should have the post-treatment visit Week 169 conducted 3 months after the last dose of Study Drug. The 3-month post-treatment evaluation period may be omitted if the patient discontinues treatment in this study, but is continuing to receive treatment with ISIS 420915 via another mechanism.

6.2 Additional Study Assessments

6.2.1 Laboratory Assessments

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

6.2.2 Congestive Heart Failure

Any patient who 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

In addition the Congestive Heart Failure supplemental eCRF pages should be completed in the eCRF.

6.2.3 Arrhythmias

Any patient who 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

In addition, the Arrhythmias supplemental eCRF pages should be completed in the eCRF.

6.2.4 Myocardial Ischemia

Any patient who 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)

In addition, the Myocardial Infarction supplemental eCRF pages should be completed in the eCRF.

6.2.5 Event-Specific Supplemental eCRF Pages

In the event of any of the following, the corresponding supplemental eCRF pages should be completed in the eCRF:

- Death
- Valvulopathy (i.e., signs, symptoms or test results suggestive of impairment of function of 1 or more cardiac valves)
- Deep vein thrombosis or pulmonary embolism
- Peripheral arterial thromboembolism
- Cerebrovascular event or transient ischemic attack
- Revascularization
- Pulmonary hypertension

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6.3 Restriction on the Lifestyle of Patients

6.3.1 Contraception Requirements

All patients of childbearing potential must refrain from sperm/egg donation and practice effective contraception from the time of signing the informed consent form until at least 3 months after their last dose of ISIS 420915.

For the purposes of this study, a woman of childbearing potential is defined as any female who has experienced menarche and who does not meet 1 of the following conditions:

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

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

For male patients:

- Effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the use of condoms together with spermicidal foam/gel/film/cream/ suppository. Male patients must also encourage their female partner to use effective contraception from the time of signing the informed consent until 3 months after the patient's last dose of ISIS 420915. Effective contraceptive for the female partner includes surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or barrier methods (female condom*, diaphragm, sponge, cervical cap) together with spermicidal foam/gel/film/cream/suppository. Male patients with partners who are pregnant must use condoms to ensure that the fetus is not exposed to ISIS 420915.

For female patients:

- Using 2 or more of the following acceptable methods of contraception:
  - Surgical sterilization (e.g., bilateral tubal ligation)
  - Hormonal contraception
    - Oral contraceptive (either combined or progestogen alone)
    - Injectable progestogen
    - Implants of etonogestrel or levonorgestrel
    - Percutaneous contraception/device
- Intrauterine contraception/device
- Combination of male condom* with female diaphragm together with spermicidal foam/gel/ film/cream/suppository

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

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6.3.2 Other Requirements

All patients will be required to fast for at least 8 hours before a blood sample is taken for the chemistry panel, PD and retinol assessments.

7. STUDY DRUG

7.1 Study Drug Description

ISIS 420915 characteristics are listed in Table 1.

ISIS 420915 is contained in stoppered glass vials or glass prefilled syringes (PFS) and will be provided to the Study Center by the Sponsor. The ISIS 420915 storage and preparation instructions will be provided by the Sponsor. For long-term storage at clinical sites, ISIS 420915 must be stored securely at 2° to 8° Celsius and be protected from light.

Table 1 Study Drug Characteristics

Study Drug	ISIS 420915
Strength	200 mg/mL
Volume/Formulation	1.5 mL solution per 3 mL vial Or 1.5 mL solution per prefilled syringe
Route of Administration	SC 1.5 mL

7.2 Packaging and Labeling

The Sponsor will provide the Investigator with packaged ISIS 420915 labeled in accordance with specific country regulatory requirements.

7.3 Study Drug Accountability

The study staff is required to document the receipt, dispensing, and return/destruction of ISIS 420915 supplies provided by the Sponsor. The Study Center must return all used and unused ISIS 420915 vials to the Sponsor or designee. All used syringes must be disposed of as per the site's hazardous waste destruction policy.

8. TREATMENT OF PATIENTS

8.1 Study Drug Administration

For each individual patient, ISIS 420915 will be administered SC as a single 1.5 mL injection once-weekly for Weeks 1 to Y5-W52. ISIS 420915 may be administered by the Study Center personnel or at home by the patient/caregiver. If ISIS 420915 is administered during a clinic or non-clinic visit, all blood samples should be drawn prior to administration. It is not necessary for ISIS 420915 to be administered during clinic visits. Ideally blood draws should occur 7 days after the previous dose. If needed, dosing instructions and training will be provided to the patient/caregiver by the Study Center personnel.

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If needed for tolerability reasons, the single 1.5 mL injection may be administered as 2 injections of smaller volume, but prior discussion with the Study Medical Monitor is encouraged.

Please refer to the Study Drug Manual provided by the Sponsor for more detailed instructions for ISIS 420915 preparation and administration.

8.2 Other Protocol-Required Drugs

All patients will take daily oral supplemental doses of the RDA of vitamin A (approximately 3000 IU or the closest approximate dose as available in the region where 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. The vitamin A supplement should be taken throughout the treatment and post-treatment evaluation periods.

8.3 Other Protocol-Required Treatment Procedures

There are no other protocol-required treatment procedures.

8.4 Treatment Precautions

No specific treatment precautions are required for this study.

8.5 Safety Monitoring Rules

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

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

Confirmation Guidance: At any time during the study (treatment or post-treatment periods), the initial clinical laboratory results meeting the safety monitoring or stopping criteria presented below **must be confirmed** by performing measurements (ideally in the same laboratory that performed the initial measurement) on new specimens. All new specimen collections should take place as soon as possible (ideally within 3 days of the initial collection).

Stopping Rule Guidance: In the event of an initial clinical laboratory result that meets a stopping criterion, patients must not be re-dosed until a confirmatory test result has been reviewed by the Study Medical Monitor. If any of the stopping criteria described in Section 8.6 are met and are confirmed, the patient will be permanently discontinued from further treatment with ISIS 420915, evaluated fully as outlined below and in consultation with the Study Medical Monitor or appropriately qualified designee, and will be entered into the post-treatment evaluation period of the study (after completing the early termination [ET] assessments). In general, patients who do not meet the stopping rules based upon retest may continue dosing. However, the Investigator and the Study Medical Monitor (or appropriately qualified designee) should confer as to whether additional close monitoring of the patient is appropriate.

Additional Guidance: If possible, a pharmacokinetic sample should be collected as soon as possible after an SAE has occurred (preferably within 2 weeks). In addition, if a patient is asked

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to return to the clinic for additional evaluations due to an AE, then a pharmacokinetic sample should be taken at the time of the unscheduled visit.

For all safety monitoring rules below "baseline" will be defined as the ISIS 420915-CS3 Day 1 value.

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.

In the event of an ALT or AST measurement that is > 3 x the upper limit of normal (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. Similarly, confirmatory measurements should also be performed if ALT or AST levels increase to 5 x ULN.

Frequency of Repeat Measurements: Patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), that are continuing to rise should have their liver chemistry tests (ALT, AST, ALP, INR, and total bilirubin) retested at least once-weekly until levels stabilize and begin to recover (ALT and AST levels become ≤ 1.2 x ULN or 1.2 x baseline value if the baseline value was > ULN).

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

1. Obtain a more detailed history of symptoms and prior and concurrent diseases
2. Obtain further history for concomitant drug use (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
3. Obtain a history for exposure to environmental chemical agents and travel
4. Total, direct, and indirect bilirubin
5. Serology for viral hepatitis (HAV IgM, HBsAg, HCV antibody, HCV mRNA, CMV IgM, and EBV antibody panel)
6. Serology for autoimmune hepatitis (e.g., antinuclear antibody (ANA), antismooth muscle antibody, type 1 anti-liver kidney microsomal antibody)
7. Serum acetaminophen-protein adducts by high pressure liquid chromatography if recent acetaminophen usage by patient

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

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Study Medical Monitor. Repetition of the above evaluations should be considered if a patient's ALT and/or AST levels reach 5 x ULN.

8.5.2 Safety Monitoring Rules for Renal Function

In the event of a confirmed (as described in Section 8.5) laboratory result meeting 1 or more of the following criteria, urinalysis (see Appendix B) will be required approximately every 2-3 weeks.*

a. Creatinine clearance by CKD-EPI < 60 mL/min/1.73 m^2

b. Creatinine clearance by CKD-EPI decrease from baseline** > 25%

c. Urine Alb/Cr ratio > 5 x ULN

d. Serum creatinine increase from baseline** > 0.5 mg/dL

* Urine collection should be performed at the same time as the protocol specified collection of serum creatinine (see Appendices A and C)

** Baseline is the study CS3 Day 1 value

In addition, the first confirmed result meeting a criterion (at any time on study) will trigger an immediate evaluation by a local nephrologist, ideally within 1-week. The following labs should be obtained immediately: fasting serum creatinine, urine culture, 24-hour urine sample for creatinine clearance and urine protein, and urine microscopy sample with nephrologist's inspection of sediment. Consideration of a dose pause (for example with a confirmed CKD-EPI decrease > 25%) should be discussed with the Study Medical Monitor. A mandatory dose pause will occur with a 24-hour urine protein result of > 2.0 g.

If a patient remains stable over time they may be moved to less frequent monitoring of urinalysis at the discretion of the Study Medical Monitor in consultation with a nephrologist and the Investigator.

If a patient meets a renal monitoring rule that is confirmed on repeat testing, the Investigator should review the patient's concomitant medications for potentially nephrotoxic agents, and carefully consider discontinuing non-essential medications. Consultation with the Study Medical Monitor is encouraged.

8.5.3 Safety Monitoring Rules for Ocular Effects

All patients should receive an ophthalmology examination by an eye specialist at Weeks 26, 52, 78, 104, 130, and 156 and twice each subsequent treatment year (26^{th} and 52^{nd} week of each year). An ERG will also be performed at Weeks 78 and 156. In addition, any patient who complains of persistent ocular symptoms compatible with vitamin A deficiency (e.g., night blindness or dry eyes) should be referred for an ophthalmology examination. If the ophthalmologist confirms the patient's symptoms are consistent with vitamin A deficiency and/or the examination reveals physical findings that are consistent with vitamin A deficiency (but do not reach the stopping rule criteria described in Section 8.6.4) then an ERG examination should be conducted and analyzed by the central reader. In addition, it is suggested that a review

of diet and supplement use and an evaluation for factors which may contribute to low vitamin A levels such as infection, alcohol consumption, and zinc and/or iron deficiency be conducted.

If an ERG is changed from baseline and shows clear signs of vitamin A deficiency as assessed by the central reader and described below, then the patient should be monitored more frequently. Frequency will be determined by the Study Medical Monitor in consultation with the Investigator and ophthalmologist.

Clear signs of vitamin A deficiency as assessed by ERG include:

a. Change from baseline > 50%, and

b. Values below normal range (if baseline values were within normal range), and

c. Changes that are approximately symmetrical between eyes (unless there is an alternative explanation for asymmetry)

Dosing with Study Drug may continue while these evaluations are being performed.

8.5.4 Safety Monitoring Rules for Platelet Count Results

Platelets will be monitored weekly throughout the treatment period and for a minimum of 6 weeks after the last dose of Study Drug (this includes early termination patients as well as patients that complete the full treatment period). For patients participating in the Post-Treatment Evaluation Period, frequency of testing after 6 weeks from the last dose of Study Drug will be determined by the Investigator in consultation with the Study Medical Monitor.

All platelet count results must be promptly reviewed by the Investigator to ensure that the count has not met the stopping rule

If for any reason there is more than 14 days between platelet values (e.g. lab report of an unreadable sample due to clumping, hemolysis, or quantity not sufficient, or a missed lab assessment), the Investigator will contact the patient to hold dosing until a new platelet value is obtained and reviewed.

If a patient's platelet counts fall below 100,000/mm^3, additional lab tests may be requested as determined by the Investigator in consultation with the Study Medical Monitor.

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

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8.6 Stopping Rules

8.6.1 Stopping Rules for Liver Chemistry Elevations

In the event of confirmed laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Study Medical Monitor,** dosing of a patient with ISIS 420915 will be stopped permanently:

1. ALT or AST > 8 x ULN
2. ALT or AST > 5 x ULN at 2 consecutive weekly measurements (not less than 7 days nor more than 10 days apart) both of which are confirmed. Treatment with ISIS 420915 may continue until the second consecutive weekly ALT or AST measurement is confirmed to be > 5 x ULN
3. ALT or AST > 3 x ULN **and** total bilirubin > 2 x ULN
4. ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or concomitant eosinophilia (> 5%)

8.6.2 Stopping Rules for Renal Function Test Results

In the event of an estimated creatinine clearance by CKD-EPI meeting any of the following criteria, a serum creatinine and 24-hour urine sample for creatinine clearance and protein should be obtained:

- CKD-EPI decrease of > 50% from baseline*
- Value < 45 mL/min/1.73 m^2 (if baseline CKD-EPI > 60 mL/min/1.73 m^2)
- Value < 30 mL/min/1.73 m^2 (if baseline CKD-EPI ≤ 60 mL/min/1.73 m^2)

* baseline is study CS3 Day 1 value

Dosing of a patient with ISIS 420915 will be stopped permanently if the 24-hour urine testing confirms any of the following values in the absence of an alternative explanation agree by a consulting nephrologist:

- urine protein is > 3.5 g
- creatinine clearance < 45 mL/min/1.73 m^2 (if baseline CKD-EPI > 60 mL/min/1.73 m^2)
- creatinine clearance < 30 mL/min/1.73 m^2 (if baseline CKD-EPI ≤ 60 mL/min/1.73 m^2)

Irrespective of whether the stopping rule is confirmed or not, the follow-up schedule and frequency of renal function monitoring after the initial event will be determined by the Study Medical Monitor in consultation with the Investigator and a renal consult will be requested.

8.6.3 Stopping Rule for Platelet Count Results

In the event of a confirmed platelet count less than 75,000/mm^3, and in the presence of major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with ISIS 420915 will be stopped permanently. The follow-up schedule for any

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events meeting this stopping criterion will be determined by the Investigator in consultation with the Study Medical Monitor.

In the event of a confirmed platelet count less than 75,000/mm^3, and in the absence of major bleeding or clinically-relevant non-major bleeding, further dosing of a patient with ISIS 420915 must be held until the platelet count returns to at least 100,000/mm^3. Weekly platelet monitoring should continue during this period. In addition, the Investigator should give consideration to collecting duplicate platelet samples for study in a local lab in parallel to the central lab if it would provide quicker access to the patients platelet count. If the platelet count was confirmed to be < 50,000/mm^3, then monitoring should be increased to daily until two successive values show improvement. The Investigator must notify the Study Medical Monitor within 24 hours of any local lab platelet results that show a level < 50,000/mm^3.

The suitability of the patient for continued dosing and the need for any modification to treatment schedule or dose (refer to Section 8.7) will be determined by the Investigator in consultation with the Study Medical Monitor and will be based on factors such as the original rate of decline in the patient's platelet count, whether any bleeding events were experienced by the patient, and the speed of recovery of platelet count upon holding of dosing.

Definition of major bleeding events:

International Society on Thrombosis and Haemostasis (ISTH) Major Bleeding:

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

Definition of clinically-relevant, non-major bleeding events:

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

8.6.4 Stopping Rule for Ocular Effects

A patient should be permanently discontinued from Study Drug if an ERG is changed from baseline and shows clear signs of vitamin A deficiency (as described in Section 8.5.3) and an

ophthalmology examination reveals significant changes from baseline in any 1 of certain physical signs (Bitot's spots, xerophthalmic ulcers, keratomalacia, or other signs and symptoms of corneal necrosis) and a consultation with the central reader has occurred**.**

8.6.5 Stopping Rule for QTc Prolongation

In the event of an ECG QTc (average of triplicates) above the thresholds described below, repeat triplicate ECGs should be performed approximately 1-hour later and further dosing should be discussed with the Study Medical Monitor:

- QTc > 500 msec (if baseline QTc ≤ 470 msec) or
- Increase in QTc value > 60 msec from baseline (all patients)

The suitability of the patient for continued dosing, the need for any modification to treatment schedule or dose (refer to Section 8.7), and the most appropriate follow-up schedule, will be determined by the Investigator in consultation with the Study Medical Monitor. Suitability of continued dosing will be based on factors such as clinical symptoms, width of QRS complex, presence or absence of paced rhythm, and the firing of a defibrillator (in the case that the patient has an implantable defibrillator). In addition, consideration should be given to an expert cardiology read of the patients' ECGs and a cardiology consult. If a patient is deemed suitable for continued dosing, more frequent ECGs will be performed, with the frequency to be determined by the Investigator and Sponsor Medical Monitor. Any additional monitoring/investigation will also be determined by the Investigator and Sponsor Medical Monitor.

8.7 Adjustment of Dose and/or Treatment Schedule

Adjustments of dose and/or treatment schedule should occur only on rare occasions. Any proposed adjustment to treatment schedule or dose level must be discussed with and approved by the Study Medical Monitor prior to initiation. If the patient remains stable after adjustment, he/she may be cautiously returned to the original dose/regimen after consultation with the Study Medical Monitor.

Patients may be dose paused in response to adverse events after consultation with the Study Medical Monitor.

8.8 Discontinuation of Study Treatment

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

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

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

Patients who discontinue from treatment are encouraged to remain in the study. Every effort should be made to complete the ET visit and the post-treatment evaluation visits which include weekly platelet and every 2-3 week serum creatinine testing for 6 weeks after the last dose of Study Drug. If the patient declines to participate in the post-treatment evaluation visit, at a minimum the ET visit procedures should be performed at the time of withdrawal (See Appendix A) and ideally within 14 days from the last dose of ISIS 420915.

8.9 Withdrawal of Patients from the Study

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

- Withdrawal of consent
- The patient is unwilling or unable to comply with the protocol
- The patient receives a liver transplant

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

- At the discretion of the Investigator or Sponsor for medical reasons
- At the discretion of the Investigator or Sponsor for noncompliance
- Significant protocol deviation
- Administrative decision by the Investigator or Sponsor
- ISIS 420915 becomes commercially available in the local country (patients in Year 4 or Year 5)
- ISIS 420915 is rejected by the regulatory authority in the local country

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 patient who withdraws consent to participate in the study will be removed from further treatment and study observation immediately upon the date of request. Patients withdrawn for any reason should be encouraged to complete the ET visit at the time of withdrawal (Appendix A).

Patients who receive a liver transplant should be encouraged to return to the clinic to complete the ET visit as soon as feasible after the transplant procedures.

8.10 Concomitant Therapy and Procedures

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

8.10.1 Concomitant Therapy

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

Allowed Concomitant Therapy

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

Disallowed Concomitant Therapy

Patients 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 his/her 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).

Doxycycline and tauroursodeoxycholic acid (TUCA) are not allowed during the treatment period unless approved by the Study Medical Monitor.

Diflunisal is not allowed at any time during the treatment period. Vyndaqel® may be allowed after 18 months at the discretion of the Study Medical Monitor.

Due to known potential adverse effects of nonsteroidal anti-inflammatory drugs (NSAIDs), 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 Study Medical Monitor prior to initiation of drugs that may affect renal function is recommended.

8.10.2 Concomitant Procedures

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

8.11 Treatment Compliance

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

The Study Center staff is required to document the receipt, dispensing, and return of ISIS 420915 supplies. Patients who self-administer ISIS 420915 at home must record treatment in a provided dosing diary that will be reviewed by the Study Center staff and monitor.

9. SERIOUS AND NON-SERIOUS ADVERSE EVENT REPORTING

9.1 Sponsor Review of Safety Information

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

9.2 Regulatory Requirements

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

IECs/IRBs will be notified of any SAE according to applicable regulations. The DSMB will be notified of any SAE as specified in the DSMB charter.

The Sponsor will evaluate the available information and decide if there is a reasonable possibility that ISIS 420915 caused the AE and, therefore, meets the definition of a SUSAR.

For ISIS 420915 "expected" events, refer to the Investigator Brochure.

9.3 Definitions

9.3.1 Adverse Event

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

9.3.2 Adverse Reaction and Suspected Adverse Reaction

An adverse reaction is any adverse event caused by ISIS 420915.

A suspected adverse reaction is any adverse event for which there is a reasonable possibility that ISIS 420915 caused the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

9.3.3 Serious Adverse Event (SAE)

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

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

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Hospitalization is defined as an admission of greater than 24 hours to a medical facility and does not always qualify as an AE.
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly or birth defect in the offspring of the patient (whether the patient is male or female)
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

9.4 Monitoring and Recording Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the study (i.e., before informed consent) should be recorded as Medical History and not recorded as AEs unless the pre-existing condition worsened. The exception is AEs from the parent study (ISIS 420915-CS2) that are ongoing at the time the patient enters this study. These should be recorded as ongoing AEs from ISIS 420915-CS2. The Investigator should always group signs and symptoms into a single term that constitutes a **single unifying diagnosis** if possible.

9.4.1 Serious Adverse Events

In the interest of patient safety, and to fulfill regulatory requirements**,** all SAEs (regardless of their relationship to ISIS 420915) should be reported to the Sponsor or designee within 24 hours of the Study Center's first knowledge of the event. The collection of SAEs will begin after the patient signs the informed consent form and stop at the end of the patient's follow-up period, which is defined as the final post-treatment visit. When the Investigator is reporting by telephone, it is important to speak to someone in person versus leaving a message. An Initial Serious Adverse Event Form should be completed and a copy should be faxed to the Sponsor or designee.

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

9.4.2 Non-Serious Adverse Events

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

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

The Investigator's opinion of the following should be documented in the Adverse Event eCRF:

9.4.3.1 Relationship to ISIS 420915

The event's relationship to ISIS 420915 is characterized by 1 of the following:

- **Related:** There is clear evidence that the event is related to the use of ISIS 420915, e.g., confirmation by positive re-challenge test.
- **Possible:** The event cannot be explained by the patient's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and ISIS 420915 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 ISIS 420915 administration and/or exposure suggests that a causal relationship is unlikely (For reporting purposes, Unlikely/Remote will be grouped together with Not Related).
- **Not Related:** The event can be readily explained by the patient's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and ISIS 420915.

9.4.3.2 Severity

The event's severity is characterized by 1 of the following:

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

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

9.4.3.3 Action Taken with ISIS 420915

Action taken with ISIS 420915 due to the event is characterized by 1 of the following:

- **None:** No changes were made to ISIS 420915 administration and dose
- **Permanently Discontinued:** ISIS 420915 was discontinued and not restarted
- **Temporarily Interrupted, restarted:** Dosing was temporarily interrupted or delayed due to the AE and restarted
- **Reduced dose:** Dosing was reduced to a lower dose
- **Reduced schedule:** Dosing frequency was reduced

9.4.3.4 Treatment Given for Adverse Event

Any treatment (e.g., medications or procedures) given for the AE should be recorded in the Adverse Event eCRF (treatment should also be recorded in 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 1 of the following:

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

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

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

9.5 Procedures for Handling Special Situations

9.5.1 Abnormalities of Laboratory Tests

Clinically-significant abnormal laboratory test results may, in the opinion of the Investigator, constitute or be associated with an AE. Examples of these include abnormal laboratory results that are associated with symptoms, or require treatment, e.g., bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac arrhythmias due to hyperkalemia. Whenever possible, the

underlying diagnosis should be listed in preference to abnormal laboratory values as AEs. Clinically-significant abnormalities will be monitored by the Investigator until the parameter returns to its baseline value or until agreement is reached between the Investigator and the Study Medical Monitor. Laboratory abnormalities deemed not clinically-significant (NCS) by the Investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator should not be deemed NCS on the laboratory sheet.

The Investigator is responsible for reviewing and signing all laboratory reports. The signed clinical laboratory reports will serve as source documents.

9.5.2 Prescheduled or Elective Procedures or Routinely Scheduled Treatments

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

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

9.5.3 Dosing Errors

ISIS 420915 errors should be documented as Protocol Deviations. A brief description should be provided in the deviation, including whether the patient was symptomatic (list symptoms) or asymptomatic, and the event accidental or intentional.

Dosing details should be captured in the Dosing eCRF. If the patient administers a dose of ISIS 420915 that exceeds protocol specifications and the patient is symptomatic, then the symptom(s) should be documented as an AE and be reported per Section 9.4.

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

9.5.4 Contraception and Pregnancy

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

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

information including delivery or termination is reported on Follow-up Pregnancy Forms and reported within 24 hours.

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

Female patients: If a suspected pregnancy occurs while on the study (including follow-up), a pregnancy test will be performed. The patient with a confirmed pregnancy will be immediately withdrawn from treatment with ISIS 420915. However, the patient will be encouraged to complete the post-treatment follow-up period of the study to the extent that study procedures do not interfere with the pregnancy. Regardless of continued study participation, the study physician will assist the patient in getting obstetrical care and the progress of the pregnancy will be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the Study Center and Sponsor may require access to the mother's and infant's medical records for an additional 8 weeks after birth.

Male patients: The progress of the pregnancy in a male patient's partner should be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, additional follow-up information may be requested for the mother and infant. Follow-up will be performed to the extent permitted by applicable regulations and privacy considerations.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Subsets, and Covariates

10.1.1 Safety Endpoints

- Adverse events
- Vital signs and weight
- Physical examination
- Clinical laboratory tests
- ECG
- Use of concomitant medication
- Ophthalmology and ERG examinations

10.1.2 Efficacy Endpoints

- Change in the mNIS+7 score and components from baseline to Week 78 and Week 156
- Change in the NIS score and components from baseline to Y5-W52 and Y4-W52
- Change in the Norfolk QOL-DN questionnaire scores from baseline to Week 78 and Week 156 and at the end of each subsequent treatment year (52nd week of each year)
- Change in the mBMI and BMI from baseline to Week 78 and Week 156

- Change in PND score from baseline to Week 78 and Week 156 and at the end of each subsequent treatment year (52nd week of each year)
- Change in GLS by ECHO from baseline to Week 78 and Week 156 and at the end of each subsequent treatment year (52nd week of each year) in the ISIS 420915-CS2 ECHO subgroup and in the Cardiomyopathy-ECHO (CM-ECHO) Set

For the mNIS+7 score, NIS score, and Norfolk QOL-DN score, the degree of progression will be estimated for the parent study period and the extension study period by treatment group of the parent study. Further details will be outlined in the Statistical Analysis Plan (SAP).

10.1.3 Pharmacodynamic Endpoints

- Change from baseline in TTR level to Week 78 and Week 156 and at the end of each subsequent treatment year (52nd week of each year)
- Change from baseline in RBP4 level to Week 78 and Week 156 and at the end of each subsequent treatment year (52nd week of each year)

10.1.4 Pharmacokinetic Endpoints

Trough ISIS 420915 plasma concentrations will be measured throughout the study. Further details of the various planned plasma PK assessments are outlined in Section 10.6.4.

10.1.5 Exploratory Efficacy Endpoints

- Change in the ECHO parameters (except GLS) in the ISIS 420915-CS2 ECHO subgroup and in the Cardiomyopathy-ECHO (CM-ECHO) Set from baseline to Week 78 and Week 156 and at the end of each subsequent treatment year (52nd week of each year)
- Change in NT-proBNP from baseline to Week 78 and Week 156 and at the end of each subsequent treatment year (52nd week of each year)
- Change in the SF-36 questionnaire scores from baseline to Week 78 and Week 156 and at the end of each subsequent treatment year (52nd week of each year)

10.2 Sample Size Considerations

No sample size calculations were performed as this is an extension study to the double-blind, placebo-controlled ISIS 420915-CS2 study. Approximately 135 patients are planned in the ISIS 420915-CS2 study and may be eligible to enroll into this study.

10.3 Populations

The Full Analysis Set will include all enrolled patients who received at least 1 injection of ISIS 420915 and who have at least 1 post-baseline efficacy assessment for the mNIS+7 score or Norfolk QOL-DN questionnaire total score.

The Safety Set will include all enrolled patients who received at least 1 injection of ISIS 420915.

The CM-ECHO set will include the subset of the 420915-CS2 Randomized Set that had a diagnosis of TTR cardiomyopathy at study entry of the parent study, but are not in the ECHO

Subgroup in the parent study, plus patients who qualified to participate in the ECHO Subgroup (whether consented or not). Patients who did not meet the criteria for the ECHO Subgroup or the CM-ECHO Set in ISIS 420915-CS2, but who are found to meet those criteria upon entry into ISIS 420915-CS3, may also be included in additional analysis (details will be found in the SAP).

The Per-Protocol Set will include the subset of the Full Analysis Set that have received at least 70% of the prescribed doses of ISIS 420915 and that have no significant protocol deviations that would be expected to affect efficacy assessments.

10.4 Definition of Baseline

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

For safety, baseline for patients on active treatment in the parent study will be the parent study baseline. For patients on placebo in the parent study, baseline for safety will be the last non-missing assessment prior to the first dose of ISIS 420915 in this study (Study Day 1) (details will be found in the SAP).

For efficacy, 2 baselines are defined for each patient: the parent study baseline and the baseline assessment in this study (details will be found in the SAP). Further details of which assessments will be considered baseline for Echo analyses for this study will be included in the SAP.

The baselines for additional analyses can be found in the SAP.

10.5 Interim Analysis

An interim analysis may be conducted when the database of the parent study is locked and unblinded. Both safety and efficacy information from this study may be summarized during this interim analysis. Additional interim analyses may be performed, with the timing of the analyses coinciding with regulatory requirements or study milestones. At Week 13 and beyond, TTR, RBP4, retinol, and NT-proBNP will be analyzed periodically using descriptive statistics.

10.6 Planned Methods of Analysis

All eCRF data, lab data transfers, mNIS+7 score data, as well as any outcomes derived from the data, will be provided in the patient data listings. Patient data listings will be presented for all patients enrolled into the study.

Descriptive summary statistics including n, mean, median, standard deviation, interquartile range (25th percentile, 75th percentile), and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data by treatment group.

All (except GLS) secondary and exploratory efficacy and pharmacodynamic endpoints will be assessed on the Full Analysis Set and Per-Protocol Set, with the former being the basis for the primary efficacy analysis. All safety assessments will be performed on the Safety Set.
PK endpoints will be assessed in the PK Set as applicable.

10.6.1 Demographic and Baseline Characteristics

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

10.6.2 Safety Analysis

Treatment duration and amount of ISIS 420915 received (including duration and amount in the parent study) will be summarized by treatment group, as well as reasons for withdrawal from ISIS 420915.

All treatment-emergent adverse events (AEs with onset after the first dose of ISIS 420915) in this study and SAEs will be summarized by the treatment group of the parent study using the MedDRA™ coding system, by system organ class, preferred term, relationship to ISIS 420915, and severity. Narratives of deaths, serious adverse events, including early withdrawals from ISIS 420915 and from study due to adverse events, will also be provided.

Laboratory tests to ensure patient safety including chemistry panel, complete blood count with differential, and coagulation panel will be summarized by study visit and by the treatment of the parent study. These safety variables will also be presented as change and percent change from baseline over time after ISIS 420915 administration, as appropriate.

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

10.6.3 Efficacy Analysis

Change from baseline to Week 78 and Week 156 and at Week 52 of each subsequent treatment year will be summarized by treatment group of the parent study for the following efficacy measures: mNIS+7 score; NIS score; Norfolk QOL DN (total score, symptoms domain score for Stage 1 patients, and physical functioning/large fiber neuropathy domain score for Stage 2 patients); mBMI and BMI; components of the mNIS+7 (NIS, heat-pain sensory, touch-pressure sensory, nerve conduction and heart rate to deep breathing tests); and PND score; and the following exploratory measures: ECHO parameters, NT-proBNP, and SF-36 questionnaire. Changes from both the parent study baseline and the extension study baseline will be summarized.

The change from parent study baseline and extension study baseline for the endpoints listed in the paragraph above will also be analyzed using a Mixed Effects Model with Repeated Measures (MMRM). Details of the MMRM will be described in the statistical analysis plan. The MMRM will be used to estimate adjusted means at each visit but no formal hypothesis tests will be performed.

For the mNIS+7 score, the degree of progression will be estimated for the parent study period and the extension study period by treatment group of the parent study. Similar summaries of progression will be performed for the components of the mNIS+7 scores, NIS scores, Norfolk QOL-DN and its domain scores.

10.6.4 Pharmacokinetic Analysis

Trough ISIS 420915 plasma concentrations will be summarized. Further details of the pharmacokinetic analysis and evaluation of immunogenicity (anti-ISIS 420915 antibodies) will be outlined in the SAP.

10.6.5 Pharmacodynamic Analysis

Change from baseline to Week 78 and Week 156 and at the end of each subsequent treatment year (52nd week of each year) will be summarized by treatment group for TTR and RBP4.

10.6.6 Additional Analyses

Not applicable.

11. INVESTIGATOR'S REGULATORY OBLIGATIONS

11.1 Informed Consent

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

Before a patient's participation in the trial, the Investigator is responsible for obtaining written informed consent from the patient after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any ISIS 420915 is administered. The patient must be given sufficient time to consider whether to participate in the study.

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

11.2 Ethical Conduct of the Study

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

11.3 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent forms, other written patient information, and any proposed advertising material must be submitted to the IEC/IRB for written approval.
A copy of the written approval of the protocol and informed consent form must be received by the Sponsor before recruitment of patients into the study and shipment of ISIS 420915. A copy of the written approval of any other items/materials that must be approved by the Study Center or IEC/IRB must also be received by the Sponsor before recruitment of patients into the study and

shipment of ISIS 420915. The Investigator's Brochure must be submitted to the IEC/IRB for acknowledgement.

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

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

11.4 Patient Confidentiality

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

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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments

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

12.2 Study Termination

The Sponsor reserves the right to terminate the study, according to the terms of the study contract. The Sponsor should notify the IEC/IRB in writing of the trial's completion or early termination. Reasons for terminating the study include, but are not limited to safety issues or emergent data from ISIS 420915 clinical studies or ISIS 420915 is rejected by the regulatory authority in the local country.

12.3 Study Documentation and Storage

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

Source documents are original documents, data, and records from which the patient's eCRF 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, eCRFs 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 Section 8 of the ICH Guidelines (E6), suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Elements should include:

- Patient files containing completed eCRFs, informed consents, and supporting copies of source documentation
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation and all correspondence to and from the IEC/IRB and the Sponsor
- If 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 eCRFs 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., eCRFs and other pertinent data) provided that patient confidentiality is respected.

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

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 eCRFs, are resolved.

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

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

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

12.5 Language

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

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

12.6 Compensation for Injury

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

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14. APPENDICES

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Appendix A Schedule of Procedures

Appendix A Schedule of Procedures

	Screen	Year 1													Year 2				Year3			
Study Week	s 4 weeks [1]	W 1	W 4	W 7	W 10	W 13	W 15	W **18**	W 21	W 23	W 26	W 29	W 39	W 52	W 65	W 78	W 91	W 104	W 117	W 130	W 143	W 156
Study Day	S-28 to S-1	D 1	D **22**	D 43	D 64	D 85	D 99	D 120	D 141	D 155	D 176	D 197	D 267	D 358	D 449	D 540	D 631	D 722	D **813**	D 904	D 995	D 1086
Visit Window (+/- Days)		0	7	7	7	7	7	7	7	7	7	7	7	7	10	10	10	10	10	10	10	10
Informed Consent	X																					
Inclusion/Exclusion	**X**																					
ISIS 420915 Admin. (weekly)2		X	**X**	X	**X**	X	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	X
Safety Assessments																						
Full Physical Exam	x3					X					**X**			**X**		**X**		**X**		**X**		X
Vital SignsA(BP[4], HR, RR, temp)	x3	X		X		X					**X**			**X**		**X**		**X**		**X**		X
ECGA(12-Lead, triplicate)	x3										X			X		X		X		X		X
ERG Exams																X						X
Ophthalmology Exams											**X**			**X**		**X**		**X**		**X**		X
AE & *Con* Meds & Concomitant procedures	**X**	X	**X**	X	**X**	X	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	X
Phone Contact[6]			**X**		**X**		**X**	**X**	**X**	**X**		**X**	**X**		**X**		**X**		**X**		**X**	

Appendix A Schedule of Procedures *Continued*

	Screen	Year 1													Year 2				Year3			
Study Week	:S 4 weeks[1]	W 1	W 4	W 7	W 10	W 13	W 15	W 18	W 21	W 23	W 26	W 29	W 39	W 52	W 65	W 78	W 91	W 104	W 117	W 130	W 143	W 156
Study Day	S-28 to S-1	D 1	D 22	D 43	D 64	D 85	D 99	D 120	D 141	D 155	D 176	D 197	D 267	D 358	D 449	D 540	D 631	D 722	D 813	D 904	D 995	D 1086
Visit Window(+/- Days)		0	7	7	7	7	7	7	7	7	7	7	7	7	10	10	10	10	10	10	10	10
Labs																						
Pregnancy Test[7]·A	X3	X		X		X					X			X		X	XS	X	XS	X	XS	X
Chemistry PanelA(fasting)	X3	X	XS	X	XS	X	XS	XS	XS	XS	X	XS	XS	X	XS	X	XS	X	XS	X	XS	X
Additional Platele 1 t a 3 nd Serum Creatinine	See visit schedule Appendix C																					
Hematologl	X3	X	XS	X	XS	X	X8	XS	XS	XS	X	XS	XS	X	XS	X	XS	X	XS	X	XS	X
UrinalysisA	X3	X	XS	X	XS	X	X8	XS	XS	XS	X	XS	XS	X	XS	X	XS	X	XS	X	XS	X
24 hour Urine (serum creatinine required)[9]	X																					
Thyroid PanelA	X3			X		X					X			X		X		X				X
PT, aPTT, INRA	X3			X		X					X			X		X		X				X
RetinolA(fasting)		X		X		X					X			X		X		X		X		X
hs-cRpA		X		X		X					X			X		X	XS	X	XS	X	XS	X
PD PanelA(fasting)		X		X		X		XS	XS		X		XS	X	XS	X	XS	X	XS	X	XS	X
NT-proBNPA		X		X		X		XS			X		XS	X	XS	X	XS	X	XS	X	XS	X
Immunogeniciif				X		X		XS			X		XS	X	XS	X	XS	X	XS	X	XS	X
PK TroughA		X		X		X		XS			X		XS	X	XS	X	XS	X	XS	X	XS	X

Appendix A Schedule of Procedures *Continued*

	Screen	Year 1													Year 2				Year3			
Study Week	:S 4 weeks[1]	W 1	W 4	W 7	W 10	W 13	W 15	W 18	W 21	W 23	W 26	W 29	W 39	W 52	W 65	W 78	W 91	W 104	W 117	W 130	W 143	W 156
Study Day	S-28 to S-1	D 1	D 22	D 43	D 64	D 85	D 99	D 120	D 141	D 155	D 176	D 197	D 267	D 358	D 449	D 540	D 631	D 722	D 813	D 904	D 995	D 1086
Visit Window(+/- Days)		0	7	7	7	7	7	7	7	7	7	7	7	7	10	10	10	10	10	10	10	10
Efficacy Assessments																						
mNIS+7 Assessment[10]											X			X		2X		X		X		2X
Norfolk QOL-DN[11]											X			X		X		X		X		X
SF-36 Questionnaire											X			X		X		X		X		X
PND Score		X									X			X		X		X		X		X
Body Weight (fasting)		X				X					X			X		X		X		X		X
Transthoracic ECH0[12]		X												X		X		X				X

Appendix A Schedule of Procedures *Continued*

	Vear4				Years				Early Term[14]	Post-Treatment Evaluation
Study **Week**	Y4-W13	Y4-W26	Y4-W39	Y4-W52	Y5-W13	Y5-W26	Y5-W39	Y5-W52		Last Dose+ 13 weeks
Study Day										
Visit Window(+/- Days)	14	14	14	14	14	14	**14**	14	7	14
Informed Consent										
Inclusion/Exclusion										
ISIS 420915 Admin. (weekly)2	**X**	X	**X**	X	**X**	X	**X**	X		
Safety Assessments										
Full Physical Exam		X		X		X		X	X	X
Vital SignsA(BP[4], HR, RR, temp)		X		X		X		X	X	X
ECGA(12-Lead, triplicate)		X		X		X		X	X	X
ERG Exams										
Ophthalmology Exams		X		X		X		X	X	
AE & Con Meds & Concomitant procedures	**X**	X	**X**	X	**X**	X	**X**	X	X	X
Phone Contact[6]	**X**		**X**		**X**		**X**			

Appendix A Schedule of Procedures *Continued*

	Year4				Years				Early Term[14]	Post-Treatment Evaluation
Study Week	Y4-W13	Y4-W26	Y4-W39	Y4-W52	Y5-W13	Y5-W26	Y5-W39	Y5-W52		Last Dose+ 13weeks
Study Day										
Visit Window (+/- Days)	14	14	14	14	14	14	14	14	7	14
Labs										
Pregnancy Test7A·		X	XB	X	XB	X	XB	X	X	X
Chemistry PanelA (fasting)	xa	X	x8	X	xa	X	xa	X	X	X
Additional Platelet and Serum Creatinine[13]	See visit schedule Appendix C									
Hematolog/	XB	X	XB	X	XB	X	XB	X	X	X
UrinalysisA	XB	X	XB	X	XB	X	XB	X	X	X
24 hour Urine (serum creatinine required)[9]										
Thyroid PanelA		X		X				X	X	X
PT, aPTT, INRA		X		X				X	X	X
RetinolA(fasting)		X		X		X		X	X	X
hs-CRPA		X	XB	X	XB	X	XB	X	X	X
PD PanelA(fasting)	XB	X	XB	X	XB	X	XB	X	X	X
NT-proBNPA	XB	X	XB	X	XB	X	XB	X	X	X
Immunogenicit/				X				X	X	X
PK TroughA		X	XB	X		X	XB	X	X	X

Appendix A Schedule of Procedures *Continued*

	Year 4				Years				Early Term[14]	Post-Treatment Evaluation
Study Week	Y4-W13	Y4-W26	Y4-W39	Y4-W52	Y5-W13	Y5-W26	Y5-W39	Y5-W52		Last Dose + 13 weeks
Study Day										
Visit Window (+/- Days)	14	14	14	14	14	14	14	14	7	14
Efficacy Assessments										
mNIS+7 Assessment[10]									2X16	
NIS				X				X	x11	
Norfolk QOL-DN[11]				X				X	X	
SF-36 Questionnaire				X				X	X	
PND Score				X				X	X	
Body Weight (fasting)									X	x1s
Transthoracic ECHO[12]									x1s	

Appendix A Schedule of Procedures *Continued*

Shaded columns represent non-clinic visits. Labs as indicated may be collected by the Sponsor's home healthcare service or by a local laboratory (with prior Sponsor approval). Patients also have the option to go to clinic for these visits.

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

1 For an individual patient, a maximum period of 4 weeks is allowed between a patient's last dose in ISIS 420915-CS2 (CS2 Week 65 visit) and initiation of dosing in this study (CS3 Day 1 visit). All screening assessments must be completed during this period. Longer periods may be considered after discussion and approval from the Study Medical Monitor

2 ISIS 420915 can be administered in the clinic or at home by the patient/caregiver. It is not necessary for ISIS 420915 to be administered on site during clinic visits. Clinic visits should occur on a dosing day, 7 days after the previous dose

3 Assessments from ISIS 420915-CS2 may be used for screening evaluation if they were obtained within 4 weeks of Study Day 1. A longer period may be considered after discussion and approval from the Study Medical Monitor

4 Blood pressure should be taken after the patient has been sitting for ≥ 5 min

5 A +/- 2-week window is given for ERG and ophthalmology examinations. The early termination ERG and ophthalmology examinations are only done if the patient discontinues treatment after ≥ 9 mo of dosing or unless deemed necessary by Investigator or Study Medical Monitor

6 To collect AEs, conmeds, and the general wellbeing of the patient

7 For females of childbearing potential only, by serum βhCG except on Day 1 by urine hCG (pre-dose)

8 To be collected by either a local laboratory (if approved by Sponsor), Sponsor appointed home healthcare service, or Study Center as arranged by the Study Center personnel

9 The 24-hour urine collection can be done any time during the screening period or during Week 1 on treatment. Serum creatinine blood draw required

10 If ISIS 420915 administration, ERG, or ophthalmology examinations are to be performed on the same day as a mNIS+7 assessment, they should be performed after the mNIS+7 assessment is complete. For the Week 78 and Week 156 visits, 2 mNIS+7 assessments will be performed on separate days. A maximum of 2 weeks from the visit (Week 78 or Week 156) will be allowed to complete both assessments

11 Norfolk QOL-DN should be the first assessment performed at the visit

12 Study Day 1 ECHO can be done any time in the screening period or up to 2 weeks after Day 1. The Day 1 ECHO is not done if the Week 65 ECHO was conducted in ISIS 420915-CS2. A +/- 2-week window is given for all other ECHOs

13 Weekly platelet and every 2-3 week serum creatinine monitoring is required throughout the treatment period and for a minimum of 6 weeks after the last dose of Study Drug (this includes early termination patients as well as patients that complete the full treatment period). The frequency of monitoring after 6 weeks from the last dose of Study Drug will be determined by the Study Medical Monitor. The visits required to collect platelets and serum creatinine not included in this table are shown in Appendix C. These visits may be completed in clinic, by home healthcare service, or by a local laboratory

14 Early termination should be performed at the time of withdrawal, ideally within 14 days from the last dose of Study Drug

15 Omit if following Year 4 or Year 5 treatment

16 Perform mNIS+7 only if early termination is from Year 1-3 treatment

17 Perform NIS only if early termination is from Year 4-5 treatment

Time (time is in reference to ISIS 420915 administration):

A Pre-dose

Appendix B List of Laboratory Analytes

Appendix B List of Laboratory Analytes

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
- Creatine kinase
- Estimated creatinine clearance (CKD-EPI)
- Total IgG
- Total IgM

Screening Tests
- FSH (women only)
- Serum βhCG
- Urine hCG

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

PD Panel[1]
- Transthyretin
- Retinol binding protein 4 (RBP4)

24-hour Urine[4]
- Creatinine
- Protein
- Albumin

Other
- Retinol[1]
- Retinyl Palmitate
- NT-proBNP[1]
- Immunogenicity (anti-ISIS 420915 antibodies)

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

Thyroid Panel
- TSH
- Free T4 (FT4)

Pharmacokinetics[2]
- ISIS 420915 levels in plasma

Inflammatory
- Hs-CRP

Urinalysis[1]
- Color
- Appearance
- Specific gravity
- pH
- P/C and Alb/C Ratios
- Protein
- Blood
- Ketones
- Urobilinogen
- Glucose
- Leukocyte esterase
- Nitrate
- Microscopic examination[3]

1 Other biomarkers may be measured at the discretion of the Sponsor. Back-up samples will be collected and stored. For transthyretin and retinol, back-up samples may be analyzed in more sensitive transthyretin or retinol assays at the discretion of the Sponsor. Back-up urine samples may be analyzed for additional renal biomarkers

2 Plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, or to assess other actions of ISIS 420915 with plasma constituents

3 Will be performed on abnormal findings (if the initial analysis is positive for protein, blood, nitrite, &/or leukocyte esterase) unless otherwise specified (to include: casts, crystals, bacteria, epithelial cells, RBC, WBC, yeast)

4 Serum creatinine blood draw required

Appendix C Additional Visits for Platelet and Serum Creatinine

Appendix C Additional Visits for Platelet and Serum Creatinine

Note: These visits do not have specified windows to allow flexibility of scheduling but with the intent that platelets are assessed each calendar week and serum creatinine every 2-3 weeks.

Year 1	Additional Visits Between Weeks 1-29																	
Study Week	2	3	5	6	8	9	11	12	14	16	17	19	20	22	24	25	27	28
Platelets	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum Creatinine																		

Year 1	Additional Visits Between Weeks 29-52																				
Study Week	30	31	32	33	34	35	36	37	38	40	41	42	43	44	45	46	47	48	49	50	51
Platelets	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum Creatinine		x		x		x		x			x		x		x		x		x		

Year 2	Additional Visits Between Weeks 52-78																							
Study Week	53	54	55	56	57	58	59	60	61	62	63	64	66	67	68	69	70	71	72	73	74	75	76	77
Platelets	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum Creatinine		x		x		x		x		x				x		x		x		x		x		

Year 2	Additional Visits Between Weeks 78-104																							
Study Week	79	80	81	82	83	84	85	86	87	88	89	90	92	93	94	95	96	97	98	99	100	101	102	103
Platelets	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum Creatinine		x		x		x		x		x				x		x		x		x		x		

Appendix C Additional Visits for Platelet and Serum Creatinine *Continued*

Year 3	Additional Visits Between Weeks 104-130																							
Study Week	105	106	107	108	109	110	111	112	113	114	115	116	118	119	120	121	122	123	124	125	126	127	128	129
Platelets	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum Creatinine		x		x		x		x		x				x		x		x		x		x		

Year 3	Additional Visits Between Weeks 130-156																							
Study Week	131	132	133	134	135	136	137	138	139	140	141	142	144	145	146	147	148	149	150	151	152	153	154	155
Platelets	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum Creatinine		x		x		x		x		x				x		x		x		x		x		

Appendix C Additional Visits for Platelet and Serum Creatinine *Continued*

Year 4	Additional Visits Between Weeks 156 to Y4-W26																							
Study Week	Y4-W1	Y4-W2	Y4-W3	Y4-W4	Y4-W5	Y4-W6	Y4-W7	Y4-W8	Y4-W9	Y4-W10	Y4-W11	Y4-W12	Y4-W14	Y4-W15	Y4-W16	Y4-W17	Y4-W18	Y4-W19	Y4-W20	Y4-W21	Y4-W22	Y4-W23	Y4-W24	Y4-W25
Platelets	x	x	x	x	x	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x
Serum Creatinine		x		x		x		x		x				x		x		x		x		x		

Year 4	Additional Visits Between Weeks Y4-W26 to Y4-W52																							
Study Week	Y4-W27	Y4-W28	Y4-W29	Y4-W30	Y4-W31	Y4-W32	Y4-W33	Y4-W34	Y4-W35	Y4-W36	Y4-W37	Y4-W38	Y4-W40	Y4-W41	Y4-W42	Y4-W43	Y4-W44	Y4-W45	Y4-W46	Y4-W47	Y4-W48	Y4-W49	Y4-W50	Y4-W51
Platelets	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum Creatinine		x		x		x		x		x				x		x		x		x		x		

Appendix C Additional Visits for Platelet and Serum Creatinine *Continued*

Year 5	Additional Visits Between Weeks Y4-W52 to Y5-W26																							
Study Week	Y5-W1	Y5-W2	Y5-W3	Y5-W4	Y5-W5	Y5-W6	Y5-W7	Y5-W8	Y5-W9	Y5-W10	Y5-W11	Y5-W12	Y5-W14	Y5-W15	Y5-W16	Y5-W17	Y5-W18	Y5-W19	Y5-W20	Y5-W21	Y5-W22	Y5-W23	Y5-W24	Y5-W25
Platelets	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum Creatinine		x		x		x		x		x				x		x		x		x		x		

Year 5	Additional Visits Between Weeks Y5-W26 to Y5-W52																							
Study Week	Y5-W27	Y5-W28	Y5-W29	Y5-W30	Y5-W31	Y5-W32	Y5-W33	Y5-W34	Y5-W35	Y5-W36	Y5-W37	Y5-W38	Y5-W40	Y5-W41	Y5-W42	Y5-W43	Y5-W44	Y5-W45	Y5-W46	Y5-W47	Y5-W48	Y5-W49	Y5-W50	Y5-W51
Platelets	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum Creatinine		x		x		x		x		x				x		x		x		x		x		

Post Treatment Evaluation	Additional Visits Between Last Dose to LD + 13 weeks					
Last Dose (LD) + Week	LD + W1	LD + W2	LD + W3	LD + W4	LD + W5	LD + W6
Platelets	x	x	x	x	x	x
Serum Creatinine		x		x		x

Official Title: An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy (FAP)

NCT Number: NCT02175004

Document Date: SAP Version 4: 27-January-2022

IONIS PHARMACEUTICALS, INC.

Statistical Analysis Plan

ISIS 420915-CS3

An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy (FAP)

Date: January 27, 2022

Final Version: 4.0

CONFIDENTIAL

Statistical **Analysis Plan Signature Page**

Ionis Pharmaceuticals, Inc.

2855 Gazelle Court

Carlsbad, CA 92010

Compound Name:	ISIS 420915
Protocol:	ISIS 420915-CS3
Study Title:	An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS420915 in Patients with Familial Amyloid Polyneuropathy (FAP)
Issue Date:	22Feb2017 (Amendment 5)

Signature: [redacted] Jan 27, 2022 Date: Jan 27, 2022

-Ph.D.

[redacted]

Ionis Pharmaceuticals, Inc.

Signature: _____ Date: Jan 27, 2022

[redacted], Ph.D.

[redacted]

Ionis Pharmaceuticals, Inc.

Signature: _____ Date: Jan 27, 2022

[redacted], Ph.D.

[redacted]

Ionis Pharmaceuticals, Inc.

Table of Contents

Abbreviations

Abbreviation/Acronym	Definition
+7	Sum 7 test. Includes measurements of nerve conduction, vibration threshold, and heart rate to deep breathing
%CV	Coefficient of variation, expressed as a percent
ACI	Applied Clinical Intelligence, LLC
ADA	Anti-ISIS 420915 antibodies
ADaM	Analysis Data Model
AE	Adverse event
AESI	Adverse event of special interest
BMI	Body mass index
CM-ECHO	Cardiomyopathy-ECHO
CI	Confidence interval
CICL	Cardiac Imaging Core Laboratory
CRO	Contract research organization
CS2 Study Day 1	The first day ISIS 420915 is administered to the patient in the parent study
CS3 Study Day 1	The first day ISIS 420915 is administered to the patient in this present OLE study
DSMB	Data and safety monitoring board
ECG	Electrocardiogram
ECHO	Echocardiogram
EDC	Electronic data capture
EOS	End of study
EOT	End of treatment
ERG	Electroretinogram
FAC	Familial amyloid cardiomyopathy
FAP	Familial amyloid polyneuropathy
FAS	Full Analysis Set
GLS	Global Longitudinal Strain
HLT	Higher level term
HP	Heat Pain
HRDB	Heart Rate to Deep Breathing
IM	Immunogenicity
Parent study	ISIS 420915-CS2
LCRIS	Local cutaneous reaction at the injection site

LLN	Lower limit of normal
LLOQ	Lower limit of quantification
LLT	Lower level term
LSS	Longitudinal Safety Set
mBMI	Modified body mass parent (requires determination of serum albumin levels; mBMI = BMI x serum albumin g/L)
MC Core	Mayo Clinic Polyneuropathy Quality Assurance Core Facility
MedDRA	Medical Dictionary for Regulatory Activities
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
MRT	Mean residence time
NCT	Nerve Conduction Test
NIS	Neuropathy impairment score
NIS+7	Neuropathy impairment score +7
NIS-C	Neuropathy impairment score – Cranial Nerves
NIS-R	Neuropathy impairment score – Reflexes
NIS-S	Neuropathy impairment score – Sensation
NIS-W	Neuropathy impairment score – Muscle Weakness
Norfolk QOL-DN	Norfolk quality of life questionnaire-diabetic neuropathy
NSC Score	Neuropathy symptoms and change score
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
OLE	Open label extension
P25	25th percentile
P75	75th percentile
PD	Pharmacodynamic
PK	Pharmacokinetic
PKS	Pharmacokinetic set
PND Score	Polyneuropathy disability score
PPS	Per Protocol Set
QTcB	QT interval corrected for heart rate interval calculated using Bazett's formula
QTcF	QT interval corrected for heart rate interval calculated using Fridericia's formula
RBP4	Retinol binding protein 4

SAE	Serious adverse event
SAP	Statistical analysis plan
SF-36	Short Form (36) Health Survey
SMQ	Standardized MedDRA query
SOC	System Organ Class
SS	Safety set
SUSARs	Suspected unexpected serious adverse reactions
TEAE	Treatment emergent adverse event
TP	Touch Pressure
TTR	Transthyretin
ULN	Upper limit of normal
VDT	Vibration Detection Threshold

Amendment History

Section	Section Title	Change
Version 1.0, dated April 07, 2017		
Version 2.0, dated February 09, 2018		
1.3	Hypotheses	Hypothesis tests for efficacy endpoints have been removed.
3.2.1	Analysis Conventions	Three statements have been removed since hypothesis tests for efficacy endpoints have been removed: • Should the randomization stratum recorded from Interactive voice-response system (IVRS) be different from the actual data recorded in eDC of the parent study, the randomization stratum recorded from IVRS will be used in the analysis. • All endpoints will beevaluated in an exploratory manner, including the endpoints where p-values or CI are presented. • All tables and figures containing models for efficacy and pharmacodynamic endpoints will present raw data from the statistical model, with footnotes indicating the model used and covariates included in the model."
3.2.1.4	Data Summary Plan	For concomitant medication, the following statement has been removed: "All medications collected in the OLEstudy are treated as Concomitant medication."

Section	Section Title	Change
3.2.3	Patient Characteristics	Missing/partial datesimputation for FAP/FAC has been modified as below: "since CRFonly collects year and month for FAP and FACDiagnosis and onset of symptoms, for calculating the duration, a day of 15th will be used if only day is missing. JULOl will be used if both day and month are missing. If the imputed date is after the date of informed consented at CS2, use the informed consented at CS2 as the imputed date. Calculate as following (a) Duration (month)= number of month (date of informed consented at CS3- date of FAPor FAC diagnosis+ 1) (b) Duration (month)= number of month (date of informed consented at CS3- date of onset of FAP or FACsymptoms+ 1)"
3.2.3	Patient Characteristics	Summaries for medications have been clarified.
3.3.2.2	Other Adverse Events of Interest	The term of "Complement activation" has been modified as "Potential complement activation".

Section	Section Title	Change
3.3.2.6	OLE Study Analysis of TEAEs	The following changes have been done: • Removing "TEAE during the safety treatment period of the OLEstudy" from summary plan since the summary will be based on on-study data but not on-treatment data. • Adding "Australasia" in Region. • Adding following: "A plot of incidence rates and relative risks for common TEAEs, with anincidence of 5% or more, by treatment group assigned in the parent study will be provided. Summary of non-serious common TEAEs, with an incidence of 5% or more, will be presented by Preferred Term. Summary tables of the number and percentage of patients with drug related bleeding TEAEs will be presented by bleeding location and Preferred Term."
3.3.3	Vital Signs, Weight, and Physical Examination Findings	The summary for weight based on the **parent study baseline** and the **OLE study baseline** have been added.
3.3.4	Laboratory Measurements	The following underlined summary has been added: "The mean value (and associated standard error) will be plotted by treatment group in the parent study .2!. by V30M TTR mutation at randomization during the parent study over visits for the following laboratory parameters: platelets, creatinine clearance by CKD-EPI, Albumin. urine AC ratio, and urine PC ratio. Summar:vfor Albumin will also be presented based on the **parent studl£baseline** and the **OLE studl£ baseline."**
3.3.4.1	Hepatobiliary Laboratory Abnormalities	The following categories have been modified by replacing "or" by "and": ii • ALT<!:3x ULN and ALT<!:2 **x ISIS 420915 baseline** • Confirmed ALT<!:3x ULN and confirmed ALT<!:2 x ISIS 420915 baseline "

Section	Section Title	Change
3.3.4.2	Platelets	The following categorieshave been added: " • Confirmed Platelet count decrease - Grade Ia [10010"9/L to< 140x 10"9/L] • Confirmed Platelet count decrease - Grade Ib [7510"9/Lto< 100x 10"9/L] • Confirmed Platelet count decrease - Grade 2 [[50 10"9/L to < 75 x 10"9/L) • Confirmed Platelet count decrease - Grade 3 [25 10"9/Lto < 50 x 10"9/L] • Confirmed Platelet count decrease - Grade 4 [< 25 x 10"9/L]" The underlined editions have been done: "Time from **Qa'l'** I **ei llilli 4 QQI§** CS3 Stud)£Da)l 1 to
		the onset of each of these events collected in the OLE study will be summarized for the patients in SS that met the criterion. Summaries including the following descriptive statistics: mean, standard deviation, median, P25, P75, and minimum and maximum. Kaplan-Meier plots for time to first event will also be provided for value< 140 x10"9/L, value< 100 x10"9/L and value < 75 x10"9/L ." The following plots have been added: "Scatter plots for nadir platlets versus the **ISIS 420915** baseline of BMI, mBMI, and weight will be provided." The following listing has been added: "A listing of patients with dose pause due to Platelet< 75 x10"9/L will also be provided."
3.3.4.3	Renal Parameters	The following summaries has been added: "Shift tables from baseline for hemoglobin will be provided using the nadir value. Categories for the shift table will be Grade O (LLN, Absent), Grade 1 (< LLN - 100.0 g/L, Mild), Grade 2 (< 100.0 - 80.0 g/L, Moderate) and Grade 3 (< 80.0 g/L, Severe)."

Section	Section Title	Change
3.4	Efficacy Analyses	The following two paragaraphs have also been removed: "P-values reported for testing of efficacy endpoints will be evaluated in an exploratory manner. No adjustment for multiple hypothesistesting will be done."; "As not all subjects will getto year 4 and 5 of the study, the efficacy analyses in section **Error! Reference source not found.** -3.4.2.2 will only be performed on the first 3 years of data. However, data from year 4 and 5 will be summarized."
3.4.2.1	Efficacy Analysis on the Change from the Parent Study Baseline	This session have been removed.
3.4.2.2	Additional Efficacy Analysis on the Change from the Parent Study Baseline	• This session number has been moved up as 3.4.2.1. • Non-parametic analysis and MMRM models have been removed. • Inferential comparison for response rate has been removed.
3.4.2.3	Efficacy Analysis on the change from the OLE Study baseline	This session have been removed.
3.4.2.4	Additional Efficacy Analysis on the Change from the OLE Study baseline	• This session number has been moved up as 3.4.2.2. • Non-parametic analysis and MMRM models have been removed. • Inferential comparison for response rate has been removed.
5.2	Interim Analysis for Day-90 Updates	A new session for describing 90-day safety udpates has been added.
Version 3.0, dated Oct 28, 2021		
5.3	Interim Analysis II	A new session for describing Interim Analysis II (data cutoff 31MAR2018)
9	Additioal Analysis and updates in Final Analysis	Add new section

Section	Section Title	Change
Appendix 1	Add NIS-LL	Two new tables for NIS-LLcalculation.
Version 4.0, dated January 27, 2021		
9	Additioal Analysis and updates in Final Analysis	Update section 9

1. Introduction

This statistical analysis plan describes the final reporting for study ISIS 420915-CS3 as per protocol amendment #5 (22 Feb 2017). It also describes the interim analyses to support the interim reporting. Any changes from these planned analyses will be stated in the clinical study report.

1.1 Study Overview

Transthyretin (TTR) is synthesized primarily in the liver and is secreted into the plasma as a 55 KD protein composed of four identical subunits of 14 KD each. A major function of TTR in the plasma is to transport retinol (vitamin A) to tissues through an association with Retinol binding protein 4 (RBP4). Transthyretin amyloidosis is a rare hereditary disease caused by mutations in the TTR protein. The disease-causing mutations destabilize the normal tetrameric structure of TTR causing its dissociation into free monomers and subsequent aggregation into insoluble fibril deposits.

These deposits are found in multiple organs including the peripheral nervous system, gastrointestinal tract and heart. They result in local damage to cells leading to a peripheral polyneuropathy (called Familial Amyloid Polyneuropathy or FAP) and a cardiomyopathy (called Familial Amyloid Cardiomyopathy or FAC). FAP can be classified into 3 stages of disease based on ambulatory status: Stage 1 – do not require assistance with ambulation; Stage 2 – require assistance with ambulation; Stage 3 – wheelchair bound (Coutinho et al. 1980). The total worldwide prevalence of FAP has been estimated at approximately 10,000 patients (Coelho et al. 2008).

ISIS 420915 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.

ISIS 420915-CS2 (the parent study) is a Phase 2/3 multicenter, double-blind, placebo-controlled study to assess the efficacy and safety of ISIS 420915 in patients with FAP. The study plans to enroll approximately 135 patients randomized 2:1 (90 ISIS 420915 to 45 placebo) to receive 300 mg ISIS 420915 or placebo. The study drug is administered 3 times during Week 1 and once weekly during Weeks 2 to 65.

The dose level and schedule in the present open label extension (OLE) study (300 mg ISIS 420915 administered once weekly) is the same dose and schedule used during Weeks 2 to 65 in the preceding parent study. Therefore, in Week 1, ISIS 420915 was administered once instead of the three times used in the parent study. Antisense oligonucleotides of this class have been safely administered intravenously and subcutaneously in multiple clinical studies at doses up to 1000 mg (Kwoh 2008) and treatment durations ≥ 6 months (Chi et al 2008; Raal et al. 2010) and > 24 months (Santos et al. 2012). The patients randomized to ISIS 420915 in the parent study receive 65 weeks (15 months) of treatment in that study followed by up to an additional 156 weeks (3 years) in the present OLE study. The safety and tolerability of the proposed 221-week dosing period is also supported by nonclinical chronic toxicology studies with ISIS 420915.

1.2 Objectives

1.2.1 Primary Objective

To evaluate the safety and tolerability of extended dosing with ISIS 420915 in patients with FAP.

1.2.2 Secondary Objectives

To evaluate the efficacy of extended dosing with ISIS 420915 based on change from baseline and progression rate, if applicable, in the following measures:

- Modified Neuropathy Impairment Score +7 (mNIS+7)
- Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) questionnaire:
  - total score (all patients)
  - symptoms domain score (Stage 1 patients)
  - physical functioning/large fiber neuropathy domain score (Stage 2 patients)
- Modified body mass index (mBMI) and body mass index (BMI)
- Neuropathy impairment score (NIS), heat-pain sensory, touch-pressure sensory, nerve conduction, and heart rate to deep breathing tests (components of mNIS+7)
- Polyneuropathy disability score (PND score)
- To evaluate the pharmacodynamic (PD) effect of extended dosing with ISIS 420915 based on change from baseline in TTR and RBP4
- Global longitudinal strain (GLS)

To evaluate the plasma trough levels of ISIS 420915.

1.2.3 Exploratory Objectives

To evaluate the change from baseline in the following measures:

- Echocardiogram (ECHO) parameters (except GLS)
- Plasma N-terminal prohormone of brain natriuretic peptide (NT-proBNP)
- Short Form (36) Health Survey (SF-36) questionnaire

1.3 Hypotheses

There are no formal study hypotheses as this is an extension study to the double-blind placebo controlled parent study.

1.4 Endpoints

Details of safety, efficacy, pharmacokinetic (PK), and PD endpoints are described in Sections 3.3 through 3.6.

2. Procedures

2.1 General Overview of Procedures

The OLE study will consist of the following periods:

- A ≤ 4-week screening assessment period
- A treatment period of up to 260 weeks
- A 3-month post-treatment evaluation period

Screening assessments include safety and specialty labs, physical exam, vital signs, electrocardiogram (ECG), adverse event (AE), concomitant medication and concomitant procedures. A maximum period of 4 weeks is allowed between a patient's last dose in the parent study (the parent study Week 65 visit) and initiation of dosing in this present OLE study (the OLE study Day 1 visit). Periods longer than 4 weeks may be considered after discussion and approval by the Study Medical Monitor. However, the intention is to minimize the treatment pause between the two studies. Ideally the first dose in this present OLE study should be administered one week after the last dose in the parent study.

Patients will report to the Study Center for evaluations and tests 5 times in Year 1 (Study Weeks 1, 7, 13, 26, 52) and 2 times in each subsequent year (26th and 52nd week of each year). Physical examination, collection of blood for measurement of safety clinical laboratory parameters and specialty labs, measurement of vital signs, and collection of AEs and concomitant medication/procedure information will be performed according to the schedule of procedures in the protocol Appendix A. The following assessments will also be performed at specified visits during the OLE study: mNIS+7, Norfolk QOL-DN questionnaire, SF-36 questionnaire, PND score, body weight, ophthalmology examination, electroretinogram (ERG), ECG, and transthoracic ECHO examination.

During Weeks 4, 10, 15, 18, 21, 23, 29, 39, 65, 91, 117, 143, Y4-W13, Y4-W36, Y5-W13 and Y5-W39 patients labs will be collected by the Sponsor appointed home healthcare service, or the Study Center as arranged by the Study Center personnel or by local laboratory with prior Sponsor approval. In addition, platelets will be collected weekly and serum creatinine will be collected every 2-3 weeks (see the protocol Appendices A and C). Patients may also be contacted by phone to collect AEs, concomitant medication, and concomitant procedure information.

The mNIS+7 assessment is conducted at Weeks 26, 52, 78, 104, 130, and 156. Norfolk QOL-DN questionnaire is conducted at Weeks 26, 52, 78, 104, 130, 156, Y4-W52, and Y5-W52. The Norfolk QOL-DN questionnaire should be the first assessment performed at these visits. If ISIS 420915 administration, ERG, or ophthalmology examinations are to be performed on the same day as an mNIS+7 assessment, they should be performed after the mNIS+7 assessment is complete. For the Week 78 and 156 visits, two mNIS+7 assessments will be performed on separate days. A maximum of 2 weeks from the visit (Week 78 or Week 156) will be allowed to complete both assessments.

For Weeks 4-52 there is a ± 7-day visit window. For Years 2-3 the visit window is ± 10-day. After Year 3 the visit window is ± 14-day. All reasonable attempts should be made to ensure compliance with the visit schedule as outlined in the schedule of procedures (the protocol Appendix A). However, if a

visit does not occur or is delayed, all subsequent visits should be calculated based on the time elapsed since Day 1 rather than from the date of the previous visit.

After completion of the treatment period, patients will enter the 3-month post-treatment evaluation period. This period consists of clinic and non-clinic visits for safety monitoring as outlined in the schedule of procedures (the protocol Appendix A and C). Weekly platelet and every 2-3 week serum creatinine testing are required for a minimum of 6 weeks after the last dose of Study Drug (this includes early termination patients as well as patients that complete the full treatment period). Patients that terminate treatment early and do not withdraw consent should have the post-treatment visit conducted 13 weeks after the last dose of Study Drug.

Patients may be allowed to take Vyndaqel® after 18 months at the discretion of the Study Medical Monitor.

2.2 Randomization & Treatment Allocation

There is no randomization in this present OLE study. All patients will receive ISIS 420915, including patients randomized to either ISIS 420915 or placebo in the parent study.

All patients will receive 300 mg ISIS 420915 given once weekly. However, patients that had a dose reduction or schedule change in the parent study may continue with the same dose or schedule in this present OLE study.

Adjustments of dose and/or treatment schedule in the OLE study should occur only on rare occasions. Any proposed adjustment to treatment schedule or dose level must be discussed with and approved by the Study Medical Monitor prior to initiation. If the patient remains stable after adjustment he/she may be cautiously returned to the original dose/regimen after consultation with the Study Medical Monitor. Patients may be dose paused in response to adverse events after consultation with the Study Medical Monitor.

2.3 Conduct

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

2.4 Data Monitoring

2.4.1 Safety Data Monitoring

Ionis Pharmaceuticals, Inc. (or designee) is responsible for processing all reported AEs. All serious adverse events (SAEs), reported to Ionis Pharmaceuticals, Inc. (or designee), are reviewed according to standard operating procedures. The medical monitor reviews all AEs and SAEs on an ongoing basis throughout the OLE study. Ionis Pharmaceuticals, Inc. (or designee) prepares and submits 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 all applicable study sites.

2.4.2 Data and Safety Monitoring Board

The independent Data and Safety Monitoring Board (DSMB) for the parent study currently also reviews the safety and tolerability of ISIS 420915 during this present OLE study as outlined in the Safety Management Plan and DSMB Charter.

Data summaries and listings are presented by treatment group of the parent study in an unblinded fashion and for all patients from both CS2 treatment groups together. These summaries are prepared by an independent statistician. No statistical comparisons across treatment groups are provided, and no hypothesis testing is done.

Further detail on the period of DSMB oversight for this study, meeting schedule, assessments to be reviewed and controlled access to data are outlined in the DSMB Charter.

2.5 Data Management

2.5.1 Case Report Form Data

BioClinica was responsible for creating the Electronic Data Capture (EDC) data entry screens, database and edit checks using definitions developed by Ionis Pharmaceuticals, Inc. A contract research organization (CRO), named TRENNIC Data Services, is responsible for the review, data management querying and locking of the database. Data are single-entered into the EDC system by the investigator site staff. Programmed edit checks (computer logic that checks the validity of the data entered and also prompts for missing data that are 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. Exceptions are the mNIS+7, Norfolk QOL-DN, SF-36, PND, NSC, and body weight information that is entered into the EDC but firewalled from review by Ionis Pharmaceuticals, Inc until the parent study is unblinded. The data are corrected or an explanation concerning the query is provided in the EDC system. For the purpose of pre-programming and data cleaning, PAREXEL (the contract research organization (CRO) performing the statistical analysis) and a firewalled data manager working at the CRO contracted to perform data management (TRENNIC Data Services) will have access to the post-baseline mNIS+7, NSC, Norfolk-QOL-DN, SF-36, PND and body weight. After all data are entered, reviewed, and queried, the database is closed and sent to the statistics group for review and for identification of protocol deviations. After any further queries that arose from this review are resolved, the database is locked. Database closing and locking will be done at the following milestones:

1. When the last patient in the parent study has completed their last assessments in the Treatment Period in the parent study. The parent study will be unblinded at this milestone. Therefore, all treatment information are available for this OLE study;
2. After all patients complete the OLE study, referred to as end of study (EOS).

Details can be found in the Data Management Plan. Additional closing and locking may be done to support additional interim analyses, with the timing of the database closing and locking coinciding with regulatory requirements or study milestones.

2.5.2 Laboratory Data

Ionis Pharmaceuticals, Inc. is responsible for the format of the laboratory electronic data transfers and the transfer schedule. Ionis Pharmaceuticals, Inc. is responsible for the review of the clinical laboratory data. Central laboratory data is not stored in the EDC system. Investigator sites have access to the data via lab reports sent directly from the laboratory or through the laboratory's web portal (in which case Investigators only have access to data from their site). To ensure maintenance of the study blind in the ongoing parent study, TTR (also called pre-albumin), RBP4, retinol (also called vitamin A), and NT-proBNP from the first 13 weeks of treatment in this present OLE study is not available to the Sponsor, Investigators, Study Center Personnel, or the patients until the parent study is unblinded.

2.5.3 Pharmacokinetics (PK) Data and Immunogenicity (IM) Data

Ionis Pharmaceuticals, Inc. is responsible for the management and review of the PK and IM data. This process involves reviewing the patient and visit identifiers (i.e., patient demographics) with the clinical data collected in the EDC system. The PK and IM data are not stored in the EDC system. Prior to the parent study unblinding, any ISIS 420915 concentration data sets and IM data sets provided to Ionis Pharmaceuticals, Inc. by the respective bioanalytical labs do not include results for samples collected prior to Week 13, nor do they include results for Unscheduled or early term (ET) samples.

2.5.4 Echocardiogram (ECHO) Data

The ECHO data is collected, analyzed and stored in a secure database by an independent CRO (Cardiac Imaging Core Laboratory and Clinical Trials Endpoints Center at the Brigham and Women's Hospital (CICL)). The sites upload the ECHO data on a secure web-portal for analysis by CICL. ECHO data is firewalled from review by Ionis Pharmaceuticals, Inc until the parent study is unblinded. For the purpose of pre-programming and data cleaning, PAREXEL and a firewalled data manager working at the CRO contracted to perform data management (TRENNIC Data Services) have access to the post-baseline ECHO data.

2.5.5 Electrocardiogram (ECG) Data

All ECG data (machine read) are entered into the Bioclinica EDC by the sites. The Bioclinica data will be used for ECG summary and analysis.

All triplicate ECG waveforms are collected and stored in a secure database by an independent CRO (Applied Clinical Intelligence, LLC (ACI)). Selected ECGs are analyzed by ACI and the resulting data captured in the ACI database as an ECG over-read database. The ECG over-read data are used to support medical monitoring and will not be used for the ECG summary and analysis.

2.5.6 Modified Neuropathy Impairment Score +7 (mNIS+7) and Neuropathy Symptoms and Change Score (NSC)

The efficacy assessment, mNIS+7 scores, will be collected and stored by an independent contract research group, Mayo Clinic Polyneuropathy Quality Assurance Core Facility (MC Core) that is under the direction of Dr. [redacted]. The Neuropathy Symptoms and Change (NSC) score is obtained during the NIS assessment procedure and is also collected and stored by MC Core. The mNIS+7 results from each site will be faxed to MC Core for processing and quality assurance. Faxed copies will be maintained in secure rooms within locked cabinets. The NIS and NSC data are stored in the RedCap (a database). The other components of the mNIS+7 (nerve conduction, sensory testing and heart rate to deep breathing) are entered by the MC Core into a firewalled portion of the study EDC system. MC Core only has access to this portion of the EDC system and the Sponsor and clinical sites do not have access to the MC Core portion of the EDC. The mNIS+7 summated score will not be shared with the sites. Up until the parent study EOT database lock and unblinding, the Sponsor will only have access to patient parent study baseline values of the mNIS+7.

2.6 Blinding

The Statistical Analysis Plan (SAP) for this OLE study will be finalized prior to the parent study unblinding. An interim analysis specified in section 5 will be performed at the parent study unblinding. At that time, all unblinded information and firewalled datasets in the parent study for this OLE study will be available.

To ensure maintenance of the study blind in the ongoing parent study, TTR, RBP4, retinol, NT-proBNP, PK and Immunogenicity data from the first 13 weeks of treatment in this present OLE study are not made available to the Sponsor, Investigators, Study Center Personnel, or the patients until the parent study is unblinded.

Derived mNIS+7 and the components including NIS, +7 and modified +7, as well as NSC, Norfolk QOL-DN, SF-36, PND, body weight and ECHO information are not made available for sponsor review until the parent study is unblinded. For the purpose of pre-programming and data cleaning, PAREXEL and a firewalled data manager working at the CRO contracted to perform data management (TRENNIC Data Services) have access to the post-baseline mNIS+7, NSC, Norfolk QOL-DN, SF-36, PND, ECHO and body weight. Details are discussed in section 5.2.

3. Analytical Plan

3.1 Statistical Design Summary

This SAP specifies the study endpoints to be analyzed, the study populations, and the methods of analysis. Section 3.2 provides general guidelines to be followed for all analyses, and covers the analysis populations, handling of missing data, and other general topics. Analyses of baseline characteristics are also covered in this section. Section 3.3 discusses the safety analyses. Section 3.4 and 3.5 specifies the efficacy and PD endpoints and methods of analysis for these endpoints. Section 3.6 covers PK analyses.

Section 4 is for the sample size justification. Section 5 presents details on the interim analyses to be conducted for this present OLE study.

The SAP concludes with a references section and appendices.

3.2 General Overview of Analyses

This SAP describes the reporting of data at the EOS for this OLE study (unless specified otherwise). Additionally, some of these data will also be reported for the purposes of the interim analyses.

3.2.1 Analysis Conventions

All reporting will be performed in SAS version 9.3 or higher.

Efficacy results will be summarized under the treatment to which patients were randomized in the parent study. Safety and PK results by treatment group of parent study will be summarized under the treatment to which patients received in the parent study. Should there be any cases after the parent study unblinding in which a patient received treatment other than what was randomized, such cases will be discussed in the OLE study report and noted in footnotes where applicable.

All electronic case report form data, lab data transfers, ECHO, ECG, and mNIS+7 score data, as well as any outcomes derived from the data, will be provided in the patient data listings. Patient data listings will be presented for all patients enrolled into the OLE study, will include all data collected during the OLE phase, and will be sorted by treatment group of parent study, patient ID, visit, and time point (where appropriate).

Central laboratory assessments will be included in the summary tables; local laboratory assessments will only be included in listings. Exceptions to the use of local laboratory assessment in summary tables are made for platelets, where summary tables will use both local and central laboratory results.

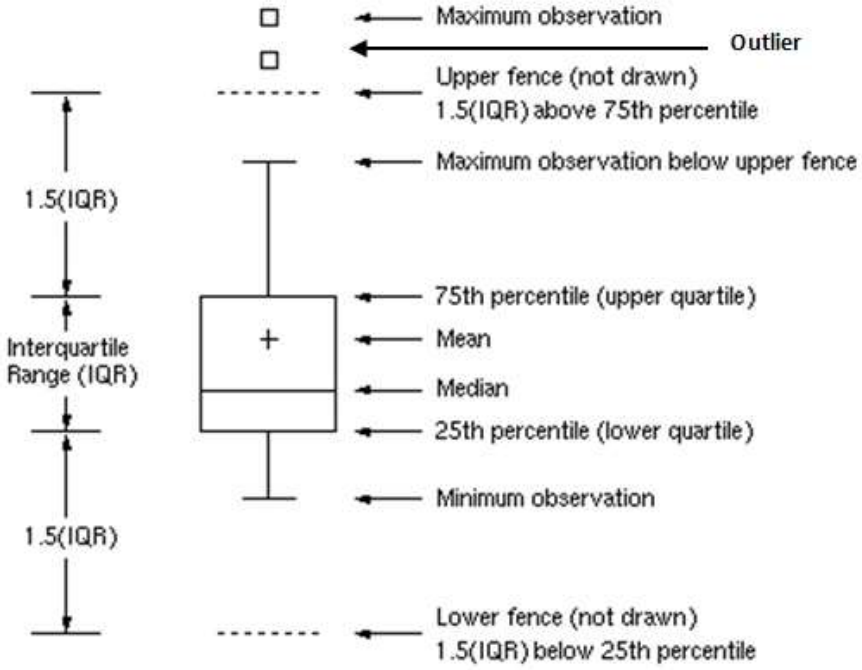
All tables will present the population frequencies in each treatment group in the parent study and/or subgroup (where appropriate) and will indicate the number of patients with non-missing data and the denominators for percentages.

Descriptive summary statistics including n, mean, percentiles (e.g., median, 25th percentile [P25], and 75th percentile [P75]), standard deviation, and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables, will be used to summarize data by treatment group of the parent study. Summaries of PK parameters, if applicable, will also present geometric mean, standard deviation of log-transformed data, and coefficient of variation, expressed as a percent (%CV). Where appropriate, p-values will be reported. All statistical tests will be conducted using 2-sided tests with a 5% Type I error rate, unless otherwise specified.

Age will be presented in years. Weight will be presented in kg. Height will be presented in cm. Temperature will be presented in ℃. Laboratory values will be summarized using standard units (SI units). Precision for displays will use the following conventions. Means, percentiles (e.g., median, P25, and P75), least squares means, difference in least squares means will be displayed to one more decimal place than measured values. Standard deviations and standard errors will be displayed to

two more decimal places than measured values. The minimum, maximum and confidence intervals (CI) will be displayed using the same number of decimal places as the recorded values. All raw values presented in listings will be displayed to the measured precision. Percentages will be displayed to one decimal place. P-values will be displayed to 3 decimal places. CI will be presented using a comma separator rather than a dash.

As shown in the schematic below, boxplots will display values from minimum to maximum within the upper and lower fences, the likely range of variation from P25 to P75 and the median. A symbol inside the box will indicate the mean. A segment inside the box will show the median and "whiskers" above and below the box will show the locations of the minimum and maximum observations within the upper and lower fences (see definition below). Individual observations outside the upper or lower fences will also be marked.



All efficacy and PD endpoints, except GLS will be assessed on the Full Analysis Set (FAS) and Per-Protocol Set (PPS). Refer to Section 3.2.2 for a description of the patient populations. Safety analysis will be performed on the Safety Set (SS) or Longitudinal Safety Set (LSS). PK endpoints will be assessed in the Pharmacokinetic Set (PKS) as applicable. ECHO endpoints including GLS will be assessed for all enrolled subjects, the ECHO subgroups and in the Cardiomyopathy-ECHO (CM-ECHO) Set.

An interim analysis of this OLE study will take place at the same time when the parent study database is locked and unblinded at EOT. Other interim analyses may be performed with the timing of the analyses coinciding with regulatory requirements or study milestones. See section 5 for details on the interim analyses. The final EOS analyses will take place after all patients have completed the study and the database has been locked.

3.2.1.1 Definitions and Computational Formulas

3.2.1.1.1 Day 1 of ISIS 420915 and CS3 Study Day 1:

- **Day 1 of ISIS 420915** will refer to the first day ISIS 420915 is administered to the patient. For patients on active treatment in the parent study, Day 1 of ISIS 420915 will be the first day ISIS 420915 is administered in the parent study. For patients on placebo in the parent study, Day 1 of ISIS 420915 will be the first day ISIS 420915 is administered in this OLE study.
- **CS3 Study Day 1** will refer to the first day ISIS 420915 is administered to the patient in this OLE study.
- **CS2 Study Day 1** will refer to the first day study drug (ISIS 420915 or Placebo) is administered to the patient in the parent study.

3.2.1.1.2 Three baselines are defined as following:

- **Parent study baseline** will be the baseline of the parent study, which is defined for most endpoints, unless specified, as the last non-missing value prior to the Day 1 of treatment, ISIS 420915 or Placebo, in the parent study. Considerations for mNIS+7, ECG, NSC, ERG and laboratory assessment are detailed below.
  - For mNIS+7 and its individual components, the **parent study baseline** will be defined as the average of two assessments taken within 60 days prior to the first dose of Study Drug. If only one assessment has been done, the single assessment will be used in place of the average. Rarely, for patient convenience, the **parent study baseline** mNIS+7 assessment(s) (or a subset of this assessment) will have been completed early in the parent study treatment period rather than pre-treatment. These assessments will be included in the analysis as valid baseline assessments provided they are taken within one week after the first dose. The rationale for this is that the pharmacology of the drug indicates that the drug will have no effect on mNIS+7 this early in treatment, and including these values as the baseline assessments will allow these patient's data to be included in the efficacy analysis. Further details of the assessment level data imputation are described in Section 3.2.1.3 of this document. Note that the NIS screening assessment can be used as one of the two assessments provided it was done within 60 days of first dose of Study Drug. Further details on how to handle missing baseline results are described in section 3.2.1.3.
  - For NSC and individual components, the **parent study baseline** will be defined as the average of two assessments taken within 60 days prior to the first dose of Study Drug in the parent study. If only one assessment has been done, the single assessment will be used in place of the average. Because NSC score is collected during the NIS assessment procedure in the parent study, it is possible it could be completed early in the treatment period rather than pre-treatment. These assessments will be included in the analysis as valid **parent study baseline** assessments provided they are taken within one week after the first dose of the parent study.
  - For ECG, the **parent study baseline** will be defined as the average of the triplicate taken on Day 1 Pre-dose in the parent study. If only one or two assessments are available, the single

assessment or average of the two assessments will be used. In the case that Day 1 Pre-dose is missing, screening visit results of the parent study will be used as baseline.

- The protocol permitted baseline ERG and ophthalmology examinations can be done up to one week after **CS2 Study Day 1**. Assessments done within one week of first dose will be included in the analysis as valid **parent study baseline** assessments.
- The **parent study baseline** laboratory assessment including PD will be defined as the average of all non-missing pre-dose assessments in the parent study.

- **OLE study baseline** will be defined as the last non-missing assessment prior to the first dose of ISIS 420915 in the OLE study (**CS3 Study Day 1**). However the last assessment must be collected within 3 months (90 days) before **CS3 Study Day 1** of OLE study in order to be used to derive the baseline, i.e. if there is no assessment within 3 months, the OLE study baseline will be missing. Depending on when the assessments are scheduled to be collected this may be derived from the **CS3 Study Day 1** or the screening visit in the OLE study or the last non-missing assessment from the parent study. Considerations for mNIS+7, NSC, and ECG are detailed below:
  - For mNIS+7 (and its individual components) and NSC (and its individual components), if the last assessment is the Week 66 assessment in CS2, the average of the two Week 66 assessments will be taken (as defined in the CS2 Statistical analysis plan). If only one assessment has been done, the single assessment will be used.
  - For ECG, the **OLE study baseline** will be defined as the average of the triplicate taken at the screening visit of the OLE study. If only one or two assessments are available, the single assessment or average of the two assessments will be used. If ECG wasn't measured at the screening visit of the OLE study, the last visit in the parent study collected within 3 months (90 days) before **CS3 Study Day 1** of OLE study will be used as baseline.
- **ISIS 420915 baseline** will be the **parent study baseline** for patients randomized to ISIS 420915 in the parent study, and will be the **OLE study baseline** for patients randomized to placebo in the parent study.

3.2.1.1.3 Three baselines for analyses:

- Efficacy analyses and PD analyses are based on **the parent study baseline** and **the OLE study baseline**. Details of separate analyses based on each baseline will be specified in the section 3.4 and 3.5.
- Safety analyses are based on **ISIS 420915 baseline**. Details of separate analyses based on each baseline will be specified in the section 3.3.
- Further details of which assessments will be considered baseline for ECHO analyses for this present OLE study are included in a separate SAP for the ECHO data.

3.2.1.1.4 On-treatment, post-treatment and on-study in either the parent study or the OLE study (Details on the planned summary/analysis at each period are discussed in the section 3.2.1.4):

- For efficacy endpoints except for BMI and mBMI:
    - The efficacy on-treatment period for the parent study spans the time during which the study treatment is administered from the **CS2 Study Day 1** until 52 days after the last dose of medication in the parent study. The efficacy on-treatment period for the OLE study is from the **CS3 Study Day 1** until 52 days after the last dose of medication in the OLE study
    - For both studies the efficacy post-treatment period starts on the day after the efficacy treatment period and ends on the day of the patient's last contact datewithin the study.
- For BMI, mBMI and PD endpoints:
    - The on-treatment period for the parent study spans the time during which the study treatment is administered from the **CS2 Study Day 1** until 28 days after the last dose of medication in the parent study. The on-treatment period for the OLE study is from the **CS3 Study Day 1** until 28 days after the last dose of medication in the OLE study.
    - For both studies the post-treatment period starts on the day after the treatment period and ends on the day of the patient's last contact date within the study.
- For safety endpoints except for ERG:
    - The on-treatment period for the parent study spans the time during which the study treatment is administered from the **CS2 Study Day 1** until 7 days after the last dose of medication in the parent study. The on-treatment period for the OLE study is from the **CS3 Study Day 1** until 7 days after the last dose of medication in the OLE study.
    - For both studies the safety post-treatment period starts on the day after the safety treatment period and ends on the day of the patient's last contact date within the study.
    - For both studies the Safety on-study period spans the time drug is first administered until the day of the patient's last contact date within the study.
    - The period for the longitudinal safety analysis spans the time from the first dose of ISIS 420915 in the parent study and ends on the day of the patient's last contact date within the study. The subject's last contact date is defined as follows:

      (1) for subjects who signed an informed consent form in the OLE study, it is the last contact date within the OLE study;

      (2) for subjects who did not sign an informed consent form in the OLE study but had been administered ISIS 420915 in the parent study, it is the last contact date within the parent study. The details of longitudinal safety analysis for AEs and safety lab results will be addressed in section 3.3.
- For ERG:
    - The on-treatment period for the parent study spans the time during which the study treatment is administered from the **CS2 Study Day 1** until 28 days after the last dose of medication in the parent study. The on-treatment period for the OLE study is from the **CS3 Study Day 1** until 28 days after the last dose of medication in the OLE study.

- For both studies the safety post-treatment period starts on the day after the safety treatment period and ends on the day of the patient's last contact date within the study.

- The PK on-study period for the OLE study spans the time ISIS420915 is administered in the OLE study (**CS3 Study Day 1**) until the day of the patient's last contact date within the OLE study.
- The Immunogenicity (IM) on-study period for the OLE study spans the time the first dose of ISIS420915 in the parent study and ends on the day of the patient's last contact date within the OLE study. This period is for defining patient IM status (Details in section 3.2.1.1.6).

3.2.1.1.5 Durations of study drug exposure and total dose of ISIS 420915:

- Durations of overall drug exposure (days) across both studies will be derived as the difference in days between the date of the last dose of ISIS 420915 and **Day 1 of ISIS 420915** plus one. For patients who are not enrolled in the OLE study, the last dose of ISIS 420915 is administered in the parent study; for patients who are enrolled in the OLE study, the last dose of ISIS 420915 is administered in the OLE study.

  The total dose of study drug during the treatment period for either the parent study or the OLE study will be computed for patients receiving ISIS 420915 by summing the dose administered between **Day 1 of ISIS 420915** and the last dose date in the parent study for patients who are not enrolled in the OLE study or the last dose date in the OLE study for patients who are enrolled in the OLE study. Total dose will be summarized in milligrams as part of longitudinal safety analysis.

- Duration of drug exposure in OLE study (days) will be derived as the difference in days between the date of the last dose of ISIS 420915 in OLE study and **CS3 Study Day 1** plus one.

  The total dose of study drug during the treatment period for the OLE study will be computed for patients receiving ISIS 420915 in the OLE study by summing the dose assigned between **CS3 Study Day 1** and the EOT date or date of early termination in OLE study. Total dose will be summarized in milligrams.

3.2.1.1.6 Immunogenicity (IM):

- For subjects with negative IM status in the parent study, the onset (T_{first}) of anti-ISIS 420915 antibodies in OLE study will be derived as difference in days between the date when first immunogenicity sample becomes confirmed positive (i.e., positive sample IM status) in OLE study and **Day 1 of ISIS 420915** plus one.
- For subjects with positive IM status in the parent study, the onset (T_{first}) of anti-ISIS 420915 antibodies in the parent study will be used as the onset of the OLE study.

3.2.1.1.7 BMI and mBMI:

- Body mass index (**BMI**) will be computed using the formula:

  $$BMI = (\text{weight in kilograms}) / [\text{height in cm} / 100]^2$$

- Modified BMI (**mBMI**) will be computed from BMI and serum albumin levels by:

  $$mBMI = BMI * \text{serum albumin (g/L)}.$$

3.2.1.2 Scoring of Assessment Instruments

mNIS+7

The mNIS+7 consists of two composite scores: the NIS composite score (maximum of 244 points) and the modified +7 composite score (maximum of 102.32 points).

NIS

The NIS composite score consists of 4 components:

- Cranial Nerves (NIS-C), maximum 40 points
- Muscle Weakness (NIS-W), maximum 152 points
- Reflexes (NIS-R), maximum 20 points
- Sensation (NIS-S), maximum 32 points.

Questions that make up each composite are listed in the table below.

NIS composite	**Question number**
Cranial Nerves	1-5
Muscle Weakness	6-24
Reflexes	25-29
Sensation	30-37

Note that each question is separately assessed for the right and left side of the body, meaning that questionnaire is comprised of 74 subcomponents (37 for the left side, and 37 for the right side).

Modified +7

The modified +7 composite score consists of 4 components:

- 1 component for autonomic nerve assessment:
  - Heart Rate to Deep Breathing (HRDB), minimum -3.72 points, maximum 3.72 points,
- 1 component for the nerve conduction assessment of the lower and upper limbs:
  - Nerve Conduction Tests ($\sum$5 NC), maximum 18.6 points from 5 subcomponents (PMAK, TMAK, UMAE, USAW, SSAB) with minimum -3.72 points and maximum +3.72 points each,
- 2 components for the sensory nerve assessment:
  - Touch-Pressure (TP), maximum 40 points
  - Heat-Pain (HP), maximum 40 points.
    NOTE: Testing for both TP and HP is done at up to 10 sites on one side of the body. To obtain the full body score for TP and HP, the summation scores from all 10 anatomical sites

is multiplied by 2 (only one side of the body is tested as FAP is symmetrical neuropathy, identical results are assumed for the other side).

Component	Data entry convention /Comment	Pre-processingstep
Heart Rate Deep Breathing	If HRDB could not be measured due to pacemaker or arrhythmia, MC Core checked either the box "no reliable data to due pacemaker" or "no reliable measure points due to arrhythmia," and left the HRDB score as blank in the BioClinica database	None
	If HRDB was not measured in error or missing for other reasons, MC Core entered a "-9" into the BioClinica database	Set "-9" to missing
	Transform normaldeviate score so that larger values coincide with worse outcomes	Multiply subcomponent score by "-1"
Nerve conduction test	If the nerve attribute was not tested in error, MCCore entered a "-9" into the BioClinica database	Set "-9" to missing
	For all 5 subcomponent (SSAB, USAW, UMAE, PMAK, TMAK) transform subcomponent normal deviate score so that larger values coincide with worse outcomes	Multiply each subcomponent score by "-1"
Touch Pressure	If an anatomicalsite was assessed, , MC Core entered a "O", "1" or "2" into the BioClinica database	None
	If an anatomicalsite was skipped because it was assumed to be< 95%, MC Core left the field blank in the BioClinica database (the last assessed more distalanatomical site has a "O" entered)	Set blank field to "O"
	If an anatomicalsite was not tested in error, MC Core entered a "-9" into the BioClinica database	Set "-9" to missing
Heat Pain	If an anatomicalsite was assessed, MC Core entered a "O", **"1"** or "2" into the BioClinica database	None
	If an anatomicalsite was skipped because it was assumed to be< 95%, MC Core left the field blank in the BioClinica database (the last assessed more distalanatomical site has a "O" entered)	Set blank field to "O"

	If an anatomical site was not tested in error, MC Core entered a "-9" into the BioClinica database	Set "-9" to missing

Additionally, for Heat Pain and Touch Pressure, the composite scores are calculated by multiplying the sum of the 10 averaged subcomponent scores (defined below) by 2.

NIS+7

The NIS+7 consists of two composite scores: the NIS composite score (above) and the +7 composite score (maximum of 26.04 points).

+7

The +7 composite score consists of 3 components:

- 1 component for autonomic nerve assessment:
  - Heart Rate to Deep Breathing (same as modified +7), minimum -3.72 points, maximum 3.72 points,
- 1 component for the peripheral nerve assessment of the lower limb:
  - Nerve Conduction Tests (LS NC nds), maximum 18.6 points from 5 subcomponents (PMAK, PMCVK, PMLA, TMLA, SSAB) with minimum -3.72 points and maximum +3.72 points each. Please note that 3 of the subcomponents used in +7 (PMCVK, PMLA, TMLA) are different from 3 of the subcomponents used in modified +7 (TMAK, UMAE, USAW).
- 1 component for the sensory nerve assessment
  - Vibration Detection Threshold (VDT), minimum -3.72 points, maximum 3.72 points.

Due to the testing algorithm and the MC Core data entry conventions, raw+ 7 data need to undergo a pre-processing step before the scores can be derived. The different pre-processing steps are summarized in the table below.

Component	Data entry convention /Comment	Pre-processing step
Heart Rate Deep Breathing	If HRDB could not be measured due to pacemaker or arrhythmia, MC Corechecked either the box "no reliable data to due pacemaker" or "no reliable measure points due to arrhythmia," and left the HRDB score as blank in the BioClinica database	None
	If HRDB was not measured in error or missing for other reasons, MC Core entered a "-9" into the BioClinica database	Set "-9" to missing
	Transform normal deviate score so that larger valuescoincide with worse outcomes	Multiply subcomponent score by "-1"

Nerve conduction test	If the nerve attribute was not tested in error, MC Core entered a "-9" into the BioClinica database	Set "-9" to missing
	For PMCVK, PMLA, TMLA, if the attribute could not be estimated/ measured due to an amplitude (CMAPS) of O in the fibular or tibial nerve, MC Core left the field blank in the BioClinica database	See imputation method for group B below
	For PMAK, PMCVK, SSAB, transform normal deviate subcomponent score so that larger valuescoincide with worse outcomes	Multiply subcomponent score by "-1"
Vibration Detection	If the vibration test was not tested in error, MC Core entered a "-9" into the BioClinica database	Set "-9" to missing

Norfolk QOL-DN

The Norfolk QOL-DN (version: 2003) consists of one composite score (Total QOL) and five sub-domain scores (physical functioning/large fiber neuropathy, activities of daily living, symptoms, small fiber neuropathy, and autonomic neuropathy). The scoring of the Norfolk QOL-DN will be conducted according to the scoring manual developed at the Eastern Virginia Medical School, and is summarized below.

Questions that make up each domain are listed in the table below

Norfolk QOL-DN Domain	Question number
physical functioning/large fiber neuropathy	8, 11, 13-15, 24, 27-35
activities of daily living	12,22,23,25,26
symptoms	1-7, 9
small fiber neuropathy	10, 16, 17, 18
autonomic neuropathy	19,20,21

All symptoms (Questions 1 to 7) are a simple inventory of symptoms of neuropathy. Each of these questions are assessed for the feet, legs, hands and arms, with presence of a symptom scored as a 1 and absence as a 0. The Question Score is calculated by summing the scores for the individual sites for the Question, with the Question Score ranging from O (no symptoms) to 4 (symptoms in the feet, legs, hands, and arms). The other Questions, except Questions 31 and 32, are scaled on a 5 point Likert scale, ranging from O ("Not a problem") to 4 ("Severe Problem"). In Question 31, "Good" is scored as 0, "Very Good" is scored as -1, "Excellent" is scored as -2, "Fair" is scored as 1, and "Poor"

is scored as 2. In Question 32, “About the same” is scored a 0, “Somewhat better” is scored a -1, “Much better” is scored a -2, “Somewhat worse” is scored a 1, and “Much worse” is scored a 2.

SF-36

The SF-36 (version: 2) consists of two composite scores, the Physical Component Summary score and the Mental Component Summary score, as well as eight domain scores (physical function, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health). The scoring of the SF-36 will be conducted using Quality Metrics Certified Scoring Software v 4.5.

NSC

The NSC questionnaire (version: 04Jan2009) consists of one total score and five domains (muscle weakness, sensory (hypo/loss of sensation), sensory (paresthesia, hyper sensation), autonomic (gastro intestinal (GI) and urinary incontinence), and autonomic (non-GI/non-urinary incontinence). The muscle weakness domain is divided into four sub-domains (head and neck, chest, upper limbs, and lower limbs). The scoring of the NSC questionnaire is described in the Appendix 2 Scoring of Assessment Instruments.

3.2.1.3 Handling of Missing or Replicated Data, Unscheduled Visits, and Early Termination Visits

Composite score: NIS score, +7 score, NIS+7 score, modified +7 score, or mNIS+7 score

Missing data imputation strategies for missing visit level data

If a patient misses a visit (or the visit is performed outside the analysis visit window), or the entire mNIS+7/NIS+7 assessment is not conducted at a visit, then the mNIS+7/NIS+7 and the composite, components and subcomponents will be considered to be missing at that visit.

Missing data imputation strategies for missing assessment level data

In the parent study, two independent assessments of mNIS+7 are planned at the baseline visit and Week 66 visit, and the early termination visit (for patients that terminate treatment early). A single mNIS+7 assessment is also planned at the Week 35 visit. In this present OLE study, two independent assessments of mNIS+7 are planned at the Week 78 and 156 visit, and the early termination visit for patients that terminate treatment early during years 1 to 3. A single mNIS+7 assessment is also planned at the Week 26, 52, 104 and 130 visit. The mean of the two replicate assessments within visit will be used for analysis of the parent study baseline, the parent study Week 66 visits (provided both visits fall in the visit window and are within 52 days of the last dose of medication), the OLE study Week 78 and 156 visit (provided both visits fall in the visit window and are within 52 days of the last dose of medication). Subcomponent scores will be averaged first. These will be referred to as the averaged subcomponent scores.

At the parent study baseline and Week 66 visit, and the OLE study Weeks 78 and 156 visit, in the event that only one subcomponent has been performed, the single subcomponent will be used in place of the mean value for that visit for the averaged subcomponent score. If both of the subcomponent values are missing, the averaged subcomponent score is missing. At the parent study

and OLE study visits where one assessment is performed, the single subcomponent will be used as the averaged subcomponent score for that visit. These values will be used in the summary of averaged subcomponent scores. The component scores will be computed by summing the averaged subcomponent scores and the composite scores will be computed by summing the component scores.

For both CS2 and CS3, two independent assessments of mNIS+7 are planned at early termination visits. If both assessments are within the same visit window, the mean of the two will be used. At early terminations, in the event that only one subcomponent has been performed, the single subcomponent will be used in place of the mean value for that visit for the averaged subcomponent score.

Imputation of missing averaged subcomponents

If a patient has completed at least part of the mNIS+7/NIS+7 at a visit then the following imputation method will be used to impute this missing assessment level data for the purposes of determining component scores for summary and analysis.

The following missing data imputation steps will be considered and will be used as described below for Groups A, B, and C:

- Step 1: If at least 50% of averaged subcomponent scores within a component are available, the missing averaged subcomponent scores will be set to equal to the mean of the patient's other non-missing averaged subcomponent scores in that component. The component score is then calculated.
- Step 2 (**Parent study baseline**): In the unlikely event that there are more than 50% of the averaged subcomponents scores within a component that are missing at baseline, the missing averaged subcomponent scores will be set to equal to mean baseline averaged subcomponent score from the parent study Randomized Set (across treatment groups). The component score is then calculated. This is the same definition as used in the parent study.
- Step 3 (OLE study baseline and CS2 and CS3 post-baseline visits): For certain components, and only under certain conditions which will be listed below, the missing averaged subcomponent scores at that visit within that component only will be set equal to the mean averaged subcomponent score among the subjects randomized to placebo in the parent study in the Randomized and Enrolled set for CS2 and CS3 respectively. The component score is then calculated. This is the same definition as used in the parent study for post-baseline visits.

  If a post-baseline assessment does not fall into the scheduled analysis windows, there is no obvious visit on which the mean subcomponent scores in the placebo group can be derived. In order to apply step 3, the following visits will be used to derive the mean scores in the placebo group:

Timing of Assessment	**Visit used for deriving the mean subcomponent scores in the placebo group***

Before Week 26	OLE baseline
Between Week 26 and Week 52	Week 26
Between Week 52 and Week 78	Week 52
Between Week 78 and Week 104	Week 78
Between Week 104 and Week 130	Week 104
Between Week 130 and Week 156	Week 130
After Week 156	Week 156
*Note: the Placebo group refers to the group of patients randomized to placebo in the parent study in the Enrolled set for CS3.	

The components of the mNIS+7 and NIS+7 are grouped into A, B and C based on the imputation step used, as follows. A detailed list of components by group can be found in Table 1– Table 3 in Appendix 1 Components and Subcomponents of the mNIS+7, and NIS+7:

- Group A: For components with multiple subcomponents except the NCT component of +7, imputation step 1 and 2 will be applied.

  If, after applying step 1 for post-baseline visits, 6 out of the 7 components of the mNIS+7 composite score (NIS-C, NIS-R, NIS-S, NIS-W, HP, TP or NCT) are available and only one is missing at that visit, then step 3 will be applied for the missing component.

  If, after applying step 1 for post-baseline visits, 4 out of the 5 components of the NIS+7 composite score (NIS-C, NIS-R, NIS-S, NIS-W, or NCT) are available and only one is missing at that visit, then step 3 will be applied for that the missing component.

  Mean averaged subcomponent score used in the imputation described in step 3 are derived from the averaged subcomponent scores before step 1 imputation among the group of patients who were randomized to placebo in the parent study.

  If, after applying steps 1-3 as appropriate, there are still missing subcomponent scores, the component score will be set to missing.

- Group B: For the NCT component of +7, it should be noted that the following 3 of the 5 subcomponents of this component may be "not evaluable" as an additional category to missing: 1) fibular nerve motor conduction velocity (PMCVK), 2) fibular nerve distal latency (PMLA), 3) tibial nerve distal latency (TMLA) (see Table 3 in Appendix 1 Components and Subcomponents of the mNIS+7, and NIS+7). These nerve conduction attributes are not evaluable when the tibial or fibular nerve amplitude is 0, therefore, these "not evaluable" results are considered informative missing results and a slightly different imputation method is applied here. The following imputation rule will be used for Nerve Conduction Tests component score of +7: The normal deviate score for PMCVK, PMLA and TMLA will be respectively set to 3.72 (the worse response)

if the recorded response was classified "not evaluable." After this, imputation step 1 and 2 will be applied.

If, after applying step 1 for post-baseline visits, 4 out of the 5 components of the NIS+7 composite score (NIS-C, NIS-R, NIS-S, NIS-W, or NCT) are available and only one is missing at that visit, then step 3 will be applied for that the missing component.

Mean averaged subcomponent score used in the imputation described in step 3 are derived from the averaged subcomponent scores before step 1 imputation among the group of patients who were randomized to placebo in the parent study.

Note that these components are *not* used in the nerve conduction component of the *modified* +7, therefore Group B only includes the NCT component of the NIS+7 and not the NCT component of the mNIS+7.

- Group C: The two components, HRDB and vibration tests, have only one subcomponent. Missing data for these averaged subcomponents score will be imputed as follows:
  - For **Parent study baseline**, the missing averaged subcomponent scores will be set to equal to the mean baseline averaged subcomponent score from the parent study Randomized Set (across treatment groups). This is the same definition as used in the parent study.
  - For OLE study baseline and CS2 and CS3 post-baseline visits, the missing averaged subcomponent scores at that visit will be set equal to the mean averaged subcomponent score among the subjects randomized to placebo in the parent study in the Randomized and Enrolled set for CS2 and CS3 respectively. If a post-baseline assessment does not fall into the scheduled analysis windows, there is no obvious visit on which the mean subcomponent scores in the placebo group can be derived. In order to derive the mean scores in the placebo group, the following visits will be used:

Timing of Assessment	**Visit used for deriving the mean subcomponent scores in the placebo group***
Before Week 26	OLE baseline
Between Week 26 and Week 52	Week 26
Between Week 52 and Week 78	Week 52
Between Week 78 and Week 104	Week 78
Between Week 104 and Week 130	Week 104
Between Week 130 and Week 156	Week 130
After Week 156	Week 156
*Note: the Placebo group refers to the group of patients randomized to placebo in the parent study in the Enrolled set for CS3.	

Composite Score

The composite scores of mNIS+7, NIS+7, modified +7, +7, and NIS will each be calculated by summing the imputed components scores. If any of the component scores after imputation is still missing within a composite, the composite score will be set as missing.

Norfolk QOL-DN Domain and Total score

- For each patient at a specific visit (defined by the analysis visit window), if at least 50% of the questions for a domain (physical functioning/large fiber neuropathy, activities of daily living, symptoms, small fiber neuropathy) are not missing or if at least one question is not missing for autonomic domain, the missing questions are imputed as follows:
    - For the **Parent study baseline**, if any question is missing at baseline, the mean value for this question at baseline from the parent study Randomized Set (across treatment groups) will be used to impute the missing baseline question value, i.e., same with the derivation in the parent study. For the symptom domain, in the case that a patient responded on a particular question (Questions 1- 7) as not a having the symptom but also marked presence of the symptom in their feet, legs, hands, or arm, the question will be set to missing and the imputation rules will be followed.
    - For the **OLE study baseline** and post-baseline visits: any missing question values will be imputed using the last observed or imputed question value (including **parent study baseline** value). For the symptom domain, in the case that a patient responded on a particular question (Questions 1- 7) as not a having the symptom but also marked presence of the symptom in their feet, legs, hands, or arm, the question will be set to missing and the imputation rules will be followed.
    - Otherwise, the total for that domain will be set to missing.

The Norfolk QOL-DN total score will be calculated by summing the imputed domain scores. If any domain score after imputation is still missing, then the Norfolk QOL-DN total score will be set to missing.

The Norfolk QOL-DN individual domain and total scores will only be calculated for visits where the patient had a Norfolk QOL-DN assessment. The individual domain and total scores are set to be missing if a patient misses the visit or does not have a Norfolk QOL-DN assessment at that visit.

NSC Domain and Total score

In the parent study, two independent assessments of NSC are planned at the baseline visit and the Week 66 visit. A single NSC assessment is planned at the Week 35 visit. In this present OLE study, two independent assessments of NSC are planned at the Week 78 and 156 visit. A single NSC assessment is planned at the Week 26, 52, 104 and 130 visit. The mean of the two replicate assessments within a visit will be used for analysis of the parent study baseline, the parent study Week 66 visits (provided both visits fall in the visit window and are within 52 days of the last dose of medication), the OLE study Week 78 and 156 visit (provided both visits fall in the visit window and

are within 52 days of the last dose of medication). The individual questions scores will be averaged first. These will be referred to as the averaged question scores.

At the parent study baseline and Week 66 visits and the OLE study Weeks 78 and 156 visit, in the event that only one question has been performed, the single question will be used in place of the mean value for that visit for the averaged question score. If both of the questions are missing, the averaged question score is missing. At the parent study Week 35 visit, the OLE study Week 26, 52, 104 and 130 visit only one assessment is performed, therefore the single question will be used as the averaged question score for that visit. The sub-domain and domain scores will be computed using the averaged question scores

Imputing Missing Assessment averaged question Scores

The following imputation rule will be applied at the domain level for the sensory (hypo / loss of sensation), sensory (paresthesia, hyper sensation), autonomic (GI and urinary incontinence), and autonomic (other than GI/urinary incontinence) domains

- If at least 50% of the averaged question scores in the domain are available, the missing questions will be set to be equal to the mean of the non-missing averaged question scores in the domain. The total domain score is then calculated from the sum of the non-missing and imputed averaged question scores in the domain
- Otherwise, the domain score will be considered to be missing

Note for the imputation of the autonomic (other than GI/urinary incontinence) component in women, questions 35 and 36 are ignored and are not included in the imputation procedure

The following imputation rule will be applied at the sub-domain level for the four muscle weakness sub-domains (head and neck, chest, upper limb, lower limb):

- If at least 50% the averaged question scores in the sub-domain are available, the missing averaged question scores will be set to be equal to the mean of the non-missing questions in the sub-domain. The total sub-domain score is then calculated from the sum of the non-missing and imputed averaged question scores in the sub-domain
- Otherwise, the sub-domain score will be considered to be missing

The total value for the muscle weakness domain score is calculated by summing the four sub-domain scores. If one or more of the sub-domain scores is missing, the muscle weakness domain score will be missing.

The total NSC score is calculated by summing the 5 domain scores. If one or more of the domain scores is missing the total NSC score will be missing.

Imputation of Missing/Partial Dates The imputation of partial or missing dates for adverse events and concomitant medications are detailed in Section 3.3.1. The imputations of partial or missing dates for duration of disease from diagnosis and duration from onset of symptoms for FAP/FAC are detailed in Section 3.2.3.

Replicated Data, Unscheduled Visits, and Early Termination Visits

When change from baseline is assessed at a post-baseline visit, unless otherwise specified, only patients with both baseline and post-baseline measurements will be included in the analyses. If baseline or post-baseline value is missing for a patient, then the change from baseline will be set to missing.

For patients who withdraw from the OLE study, all data will be reported prior to the point of withdrawal in line with the population definitions and the specified analysis.

For data that are scheduled to be measured in duplicate or triplicate, the mean value of the patient will be used in tables and figures, while all measured values will appear in the listings.

If more than the scheduled number of measurements is taken, the mean will include all replicate measurements.

Analysis Visit Windows

- The efficacy and PD data will be assigned to a visit according to the visit windows in the table 1 of Appendix 3 Analysis Visit Windows. Because mNIS+7 may be implemented over several days, window definitions are based on the study day the assessment was initiated. Efficacy assessments (except BMI and mBMI) that occurred more than 52 days after the last dose of Study Drug in either parent study or the OLE study will not be included in the efficacy analysis/summaries during the efficacy on-treatment period, even if they occurred within one of the visit windows. PD assessments, as well as BMI and mBMI, that occurred more than 28 days after the last dose of Study Drug in either parent study or the OLE study will not be included in the PD analyses/summaries during the PD on-treatment period, even if they occurred within one of the visit windows. For patients who have multiple visits within a window the visit nearest the target day will be used unless two visits are equally near, in which case the average will be used. Note that if there are multiple visits within a window with some being from the post-treatment evaluation period of either the parent study or the OLE study, the visits from the post-treatment evaluation period will not be used. For mNIS+7 at baseline and Week 66 of the parent study or at Week 78 and 156 of the OLE study, the two assessments are averaged (provided both assessments are within the visit window and are within 52 days of the last dose of medication).
- Efficacy and PD data collected during the post-treatment period will be summarized with respect to the elapsed time from last dose. Assessments will be slotted into follow-up visit windows according to elapsed time from last dose based on the scheduled assessments during the post-treatment evaluation period of the study. The planned windows for this investigation are shown in the table 2 of Appendix 3 Analysis Visit Windows.
- Visit based safety assessments (scheduled and unscheduled) will be assigned to a visit according to analysis visit windows in the table 3 of Appendix 3 Analysis Visit Windows, even if they occurred within one of the visit windows. Except for platelet assessments from the local laboratory, local laboratory assessment will not be assigned to a visit and the nominal visit only will be presented in the listings. Safety assessments that occurred during the safety post-treatment period (i.e., more than 7 days after the last dose of study drug) will not be included in

the visit based safety analyses during the safety treatment period. If there are multiple visits within a window, the visit nearest the target day will be used unless two visits are equally near, in which case the average will be used. Note that safety assessments that are not utilized in the visit based summary tables will appear in listings and be used in the determination of treatment-emergent shifts or abnormalities.

- To assess the impact of treatment discontinuation on safety parameters, data from visit based safety assessment in the post treatment phase may also be summarized with respect to the elapsed time from last dose. Assessment will be slotted into follow-up visit windows according to elapsed time from last dose based on the scheduled assessments during the post-treatment evaluation period of the study. The planned windows for this investigation are shown in the table 4 of Appendix 3 Analysis Visit Windows.

3.2.1.4 Data Summary Plan

The table below details what data will be included in the summary and analysis output by endpoint type. Data summarized or analyzed at each interim analysis will be based on data collected up to the data cut date. It is possible that on-treatment data and post-treatment data available for each interim analysis is different from the final analysis at the end of study because data collected after each interim analysis data cut may slot into different treatment period. Outputs will be updated for each interim analysis and for the final analysis. In select instances the data for a type of endpoint that is summarized or analyzed may not be consistent with the rules in the table below; such exceptions will be noted in this document.

Endpoint type	Output type	Comment/definition
Efficacy	-Listings -On-treatment (CS2&CS3) summary/analysis tables -Post-treatment summary tables	-On-treatment (CS2 period):The **CS2 Study Day 1** S Date of assessment S Last dose date in parent study+ 52 days -On-treatment (CS3 period): **CS3 STUDY DAY 1** $ Date of assessment S Last dose date of OLE study+ 52 days - showing both CS2 visits and CS3 visits. Note the results of the analyses at the CS2 visits will not be the same as the results from the CS2 study as this table only includes patients in the CS3 FAS.-Post-treatment: Date of assessment > last dose date of OLE study + 52 days -Visit defined by analysis visit window
PD, BMIand mBMI	-Listings -On-treatment (CS2&CS3) summary/analysis tables -Post-treatment summary tables	-On-treatment (CS2 period): The **CS2 Study Day 1** S Date of assessment S Last dose date in parent study+ 28days -On-treatment (CS3 period): **CS3 STUDY DAY 1** S Date of assessment S Last dose date of OLE study+ 28days - showing both CS2 visits and CS3 visits. Note the results of the analyses at the CS2 visits will not be the same as the results from the CS2 study as this table only includes patients in the CS3 FAS.

Endpoint type	Output type	Comment/definition
		-Post-treatment: Date of assessment> last dose date+ 28days -Visit defined by analysis visit window
Safety Endpoints: ECG, Lab, vitals sign (including body weight)	-Listings -On-treatment summary tables (CS3) -Post-treatment summary tables	-On-treatment (CS3 period): **CS3 Study Day Is** Date of assessment *5* Last dose date + 7 days -Post-treatment: Date of assessment> last dose date+ 7 days -Visit defined by analysis visit window
Safety Endpoints: ERG and ophthalmology examinations	-Listings -On-treatment summary tables (CS3) -Post-treatment summary tables	-On-treatment (CS3 period): **CS3 Study Day** ls Date of assessment *5* Last dose date+ 28 days -Post-treatment: Date of assessment> last dose date+ 28 days -Visit defined by analysis visit window
Safety Endpoints: abnormal lab, worst ECG, meeting Stopping rule	-Listings -On-study summary tables (CS3)	-Abnormal lab analyses described in Sections 3.3.4.1 to 3.3.4.3 include post-baseline data collected from **CS3 Study Day 1** up to the day of the patient's last contact date within the study
Safety Endpoints: AE	-Listings -On-treatment (CS3) summary tables -On-study (CS3) summary tables	-On-treatment: **CS3 Study Day** ls Date of assessment *5* Last dose date + 7 days -On-study summary tables includes all **treatment emergent adverse event** (TEAE) in the OLE study, including those with onset dates> last dose date + 7 days
Selected Safety Endpoints: abnormal lab and AEs	- Longitudinal safety summary for overall parent study and OLEstudy	- Longitudinal safety summary for overall parent study and OLE study include data collected from the first dose of ISIS 420915 in the parent study and ends on the day of the patient's last contact date within the study, (1) for subjects who enrolled in the OLE study, it is the last contact date within the OLE study; (2) for subjects who are not enrolled in the OLE study but had been administered ISIS 420915 in the parent study, it is the last contact date within the parent study.
Concomitant medications	-Listings -On-treatment (CS3) summary tables -On-study (CS3) summary table	-On-treatment: **CS3 Study Day** ls Date of assessment s Last dose date + 7 days -On-study summary tables includes all concomitant medication in the OLE study, including those with onset dates > last dose date+ 7 days
lmmunogenicity	-Listings -On-study (CS2 and CS3)	-On-study summary/analysis tables include data collected from the **CS2 Study Day 1** up to the day of the

Endpoint type	Output type	Comment/definition
	summary/ analysis tables	patient's last contact date within the study (showing both CS2 visits and CS3 visits) -Visit defined by analysis visit window.
PK	-Listings -On-study (CS3) summary/ analysis tables	-Summary/analysis tablesinclude data collected from **CS3 Study Day 1** up to the day of the patient's last contact date within the study -PK concentration will be summarized based onnominal scheduled visits (showing CS3 visits)

3.2.1.5 Multicenter Studies

Approximately 135 patients are planned for the parent study may be eligible to enroll into this OLE study. Adjustment for investigative site in multivariable analyses is not planned.

3.2.2 Patient Populations Analyzed

The following analysis populations are defined for this present OLE study:

- Screened patients will be defined as patients who signed an informed consent form.
- Enrolled patients will be defined as patients who signed an informed consent form and were not screen failures.
- The FAS will include all enrolled patients who received at least 1 injection of ISIS420915 in the OLE study and who have at least one post-baseline efficacy assessment for the mNIS+7 score or Norfolk QOL-DN questionnaire total score collected after CS3 Study Day 1 in this OLE study. This will be the primary population for analysis of efficacy and PD outcomes.
- The Safety Set (SS) will include all enrolled patients who received at least 1 injection of ISIS 420915 in the OLE study. This population will beused for analyses of all safety measures collected in this OLE study. Results will be summarized under the treatment which the patients received in the parent study.
- The Longitudinal Safety Set (LSS): will include all patients who received at least 1 injection of ISIS 420915 in the parent study. This population will beused for the longitudinal safety analysis for either the parent study or this OLE study. Results will besummarized under the treatment which the patients received in the parent study. Note that this population will include patients who receive ISIS 420915 in the parent study but did not enter this OLE. It does not include patients who took placebo in CS2.
- The PPS will include the subset of the Full Analysis Set that have received at least 70% of the prescribed doses of ISIS 420915 in this OLE study and that have no significant protocol deviations in the OLE study that would be expected to affect efficacy assessments. Prescribed doses of ISIS420915 mentioned above is defined as the total assigned dose in mg from the Week 1 to the last dose within this study up to week 156 (first three years), i.e. 300mg*156 doses= 46800mg. Patients in FAS of this OLE study but excluded from PPS in the parent study will be excluded from the PPS in this OLE study as well. This will be a secondary population for

efficacy and PD analyses. The detailed criteria and definitions for major protocol violations will be specified. Results will be summarized under the treatment which the patients received in the parent study.

- The PK Set will include all enrolled patients who received at least one dose of ISIS 420915 in the OLE study and have at least one evaluable PK sample collected and analyzed with reportable result in the OLE study. This population will be used for PK analyses. Results will be summarized under the treatment which the patients received in the parent study.
- The ECHO subgroup in the parent study will include the subset of the Randomized Set that qualified and consented for the ECHO sub study in the parent study. The ECHO subgroup in this OLE study will include the ECHO subgroup patients who are enrolled in this OLE study. Results will be summarized under the treatment to which patients were randomized in the parent study.
- The CM-ECHO set in the parent study will include the subset of the Randomized Set that meet at least one of the following criteria, 1) diagnosis of TTR cardiomyopathy at study entry, or 2) eligible to participate in the ECHO Subgroup in the parent study (whether consented or not). The CM-ECHO set in this OLE study will include the CM-ECHO set patients from the parent study who are enrolled in this OLE study. Results will be summarized under the treatment to which patients were randomized in the parent study.
- The CS3 ECHO Set will include the subset of the CS3 Enrolled Set who were not in the CM-ECHO Set in the parent study, and were randomized to placebo in the parent study and had an OLE study baseline value of either interventricular septum thickness ≥ 1.3 cm or posterior wall thickness ≥ 1.3 cm.

All efficacy and PD endpoints (except ECHO parameters) will be assessed on the FAS and PPS. All safety assessments for this OLE study will be performed on the Safety Set. The longitudinal safety analysis will be performed on the Longitudinal Safety Set. PK endpoints will be assessed in the PK Set as applicable.

3.2.3 Patient Characteristics

Patients disposition, including reasons for permanent discontinuation from ISIS 420915 or withdrawal from follow-up, and number of patients in each analysis population (FAS, PPS, SS, LSS, PKS, ECHO Subgroup, CM-ECHO Set), will be summarized by treatment group of the parent study and overall for all enrolled patients.

Patient'sallocation by investigative site will be tabulated by parent study treatment group and overall for the all enrolled patients.

Protocol deviations in OLE study will be listed and summarized by deviation category.

The following patients'demographic characteristics will be summarized by treatment group of the parent study and overall for the SS, FAS, PPS, PKS, CM-ECHO Set and ECHO subgroups:

- Sex, race, ethnicity, TTR genotype

- Age at the parent study screening and age at the OLE study screening
- Duration derived from the informed consent form signed date in the OLE study, including duration of disease from FAP diagnosis (months) and duration from onset of FAP symptoms (months)

Number and percent of enrolled patients within each of the 3 randomization strata from the parent study (previous treatment with Vyndaqel® or Diflunisal; disease stage; V30M TTR mutation) will be summarized by treatment group of the parent study and overall for the SS, FAS, PPS, PKS, CM-ECHO Set and ECHO subgroups.

The following will be provided for both **parent study baselines** and **OLE study baselines** defined in section 3.2.1.1 and for the SS, FAS, PPS, PKS, CM-ECHO Set and ECHO subgroups:

Baseline severity of illness, including the NIS score, NIS+7, mNIS+7, PND score, mBMI, BMI, weight, height, and NT-proBNP will be summarized by parent study treatment group and overall. Measures of quality of life and level of functioning, including the baseline Norfolk QOL-DN total score and pre-dose SF-36 will also be included. Disease history collected in the parent study will be summarized for analysis sets defined above: Information on familial amyloid cardiomyopathy (FAC) will be summarized, including FAC diagnosis (Y/N) at parent study screening, duration of disease from FAC diagnosis (months), duration from onset of FAC symptoms (months), and clinical or laboratory criteria used to document the diagnosis of TTR cardiomyopathy.

Missing/partial dates (month and year) for the duration of disease from diagnosis for FAP/FAC and duration from onset of symptoms for FAP/FAC will be imputed as follows: since CRF only collects year and month for FAP and FAC Diagnosis and onset of symptoms, for calculating the duration, a day of 15th will be used if only day is missing. JUL01 will be used if both day and month are missing. If the imputed date is after the date of informed consented at CS2, use the informed consented at CS2 as the imputed date. Calculate as following

(a) Duration (month) = number of month (date of informed consented at CS3- date of FAP or FAC diagnosis + 1)

(b) Duration (month) = number of month (date of informed consented at CS3- date of onset of FAP or FAC symptoms + 1)

Exposure to Study Drug in OLE study will be summarized by treatment group of the parent study for the SS by durations of drug exposure in OLE study (days), total number of dose received, and total dose administered (in milligrams). Across all visits, number of subjects with dose pauses and reasons for dose pause will be tabulated. A listing presenting for each subject the number of dose reductions (frequency of administered dose < protocol defined dose, i.e. 300 mg) and missed doses (injection not givens) will be provided. Doses that were not given because the patient discontinued will not be summarized.

Overall drug exposure from the start of the parent study to the end of the OLE study will be summarized for patients who took ISIS 420915 in the parent study, i.e. LSS.

Medical history and baseline physical examination findings collected in the OLE study will be listed depending on the data availability.

Medications will be coded using WHO Drug Dictionary. The final version used will be designated in the clinical study report. Concomitant medications used will be summarized by treatment group for the SS and the CM-ECHO Set.

All medications including concomitant medications will also be listed in a by patient listing. In the listing, medications which are started before the **CS3 Study Day 1** will be marked.

Patients with any anti-platelet or anti-coagulant medication taken at any time during this study will be presented in a listing.

A concomitant medication is defined as any medication taken whilst investigational product is being taken in this study.

If a partial date is recorded in the case report form, the following convention will be used to assign the medication:

- if the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month
- if the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month.

The recorded partial date will be displayed in listings.

The definitions for on-treatment and on-study concomitant medication defined relative to use of the investigational product are shown schematically in the diagram below.

			CM	
Scenario	On-treatment	Post-treatment	On-treatment	On-study
1	x ---------- x		Y	Y
2	x ---------- x		Y	Y
3		x---- x	N	Y
4	? ---------- x		Y	Y
5	? ----------x		Y	Y
6	x---------- ?		Y	Y
7		x -----?	N	Y

CM –concomitant medication

x = start/stop date/time

? = missing date/time

3.3 Safety Analyses

All safety endpoints will be summarized for the OLE study SS. In patient listings, **ISIS 420915 baseline** values and information collected in the OLE study will be displayed. In addition, longitudinal safety analysis of selected safety endpoints for LSS will be performed for patients on ISIS 420915 in the parent study.

Safety endpoints include the following:

- Adverse events
- Vital signs and weight
- Physical examination
- Clinical laboratory tests
- ECG
- Ophthalmology and ERG examinations

3.3.1 Imputation of Missing/Partial Dates

The following imputation rules will be applied to impute AE start dates under conservative principles. If the month, year, and day are missing, the adverse event start date will be imputed as the treatment start date. If month and day are missing and year is available and is the same year as in treatment start date, the month and day from the treatment start date will be used to impute the missing month and day for the adverse event start date. Otherwise, missing month and day will be imputed as January 01. If day is missing and month and year is available and the month and year are the same month and year in treatment start date, the day from the treatment start date will be used to impute missing day for the adverse event start date. Otherwise, missing day will be imputed as 01.

Note: Treatment start date mentioned above is CS3 Study Day 1 in general. In addition, special considerations should be given to AEs which started in the parent study but continued at the time the patient enrolled in the OLE study. If the AE was originally recorded in the CS2 database, the treatment start date mentioned above is from CS2 but not CS3 Study Day 1.

3.3.2 Adverse Events (AEs)

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA). The final version used will be designated in the clinical study report. For each AE, the severity level of the event (mild, moderate, or severe) will be determined by physician opinion.

TEAEs are defined as adverse events that first occurred or worsened after the first dose of Study Drug (ISIS 420915 or Placebo). This is the general definition of TEAEs. A detailed definition of TEAEs for safety analysis of the OLE study or for the longitudinal safety analysis will be discussed in section 3.3.2.6 or in section 3.3.2.7, respectively.

In this section, whenever first dose of ISIS 420915 is used, it refers to **CS3 Study Day 1** for OLE study analysis and **Day 1 of ISIS 420915** for longitudinal safety analysis.

An AE with a completely missing start date will be assumed to be treatment emergent.

If the maximum severity of the adverse event is greater than the baseline severity, i.e. severity prior to the first dose of ISIS 420915, or if the onset date/time is the same as or after the date/time of the first dose of ISIS 420915, then the event is considered to be treatment emergent.

In the situation where change in severity (but no change in seriousness) occurs for an adverse event, study sites are instructed to enter an end date and start a new record for the adverse event. In the new record, the changed severity is to be recorded and the start date will be set to be the end date of the previous record. Data linking those records are collected in the database. Consider three scenarios:

- The first AE record occurs prior to the first dose of ISIS 420915, the second AE record occurs on or after the first dose of ISIS 420915, and the severity increases: Only the second record will be counted as treatment-emergent.
- The first AE record occurs prior to the first dose of ISIS 420915, the second AE record occurs on or after the first dose of ISIS 420915, and the severity decreases: Neither record will be counted as treatment-emergent.
- Both records occur on or after the first dose of ISIS 420915: 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.

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

In addition, special considerations should be given to AEs which started in the parent study but continued at the time the patient enrolled in the OLE study. These situations may occur if the outcome of the AE is "Ongoing" or the stop date is missing in the parent study. Records for these AEs will be created in the OLE study database with a different AE index number so that they can be updated with information collected in the OLE study, e.g. stop date and treatment. The following rules describe how these AEs will be handled in the OLE study analysis for SS and the longitudinal safety analysis for LSS:

- For AEs with the same Lower level term (LLT), complete start date and severity recorded in both the parent study and the OLE study: keep the record in the OLE Analysis Data Model (ADaM) dataset, but this record is not considered treatment emergent in CS3. In the longitudinal safety analysis, this record will be counted once (it is considered treatment emergent in CS2 and therefore considered treatment emergent in the longitudinal safety analysis).

Note that an event which started during the gap period between the parent study and the OLE study will not be considered treatment emergent in the CS3 analysis, unless the severity of the event has increased after the first dose in CS3. Such events will be regarded as treatment emergent in the

longitudinal safety analysis (see below) conducted on the LSS. Since subjects randomized to placebo in the parent study are not included in the LSS, if a placebo subject from the parent study experiences such an event, that event will not be summarized in any of the CS2, CS3 or longitudinal safety analyses.

A listing will be provided stating which patients reported each preferred term. Adverse events in the following categories will be summarized separately:

- Adverse events of special interest
- Other adverse events of interest

Summary tables of the number and percentage of patients with these adverse events will be displayed split by AEcategory and treatment group. TEAEs of special interest and other TEAEs of interest will also be summarized for patients in the CM-ECHO Set.

3.3.2.1 Adverse Events of Special Interest (AES/)

Adverse events of special interest (AESI) are those that require special collection and/or reporting. They are not necessarily those expected to be related to study drug or those most frequently occurring.

The following adverse events have been identified as an important medical risk:

AESI	Definition
Ocular adverse *events* related to vitamin A deficiency	• AE with Higher level term (HLT): Fat soluble vitamin deficiencies and disorders; or • AE with PT: Vitamin A decreased; or • AE with PT: Vitamin A abnormal; or • AE within the Structured MedDRA query (SMQ): Optic *nerve* disorders; or • AE within the SMQ: Corneal disorders; or • AE within the SMQ: Retinal disorders.
Thrombocytopenia	• AE with HLT: Thrombocytopenias; or • AE with HLT: platelet analyses
Renal Impairment	AE within theSMQ: Acute renal failure

3.3.2.2 Other Adverse Events of Interest

The following list includes other adverse events that have been identified to be of interest:

Other AEs of interest	Definition
Coagulation abnormalities	AE with HLT: Coagulopathies
Abnormal liver function	AE within the SMQ: Drug related hepatic disorders - comprehensive search
Adverse *events* at the injection site	• AE with HLT: Injection site reaction; or • AE within HLT: Administration site reaction NEC.
Flu-like symptoms	• AE with PT: Influenza like illness; or

Other AEs of interest	Definition
	• AEwith PT: Pyrexia (or Feeling hot or Body temperature increased) plus at least one of the following symptoms: o Chills o Myalgia o Arthralgia o Malaise o Fatigue o Headache o Nausea Note that only events that start on the day of the injection or the day after injection will be included. AEs with partial or missing dates will be handled as follows. First establish whether the event is treatment emergent. If yes, then establish if the preferred terms match the ones listed in the flu-like symptoms definition. If yes, check whether the event onset dates are within the specified time frame. If at this stage, onset date is missing or partially missing, the event will be considered to have started within the required time frame.
CNS disorders	AE within **System Organ Class** (SOC): Nervous system disorder
Haemorrhages	AE within the SMQ: Heamorrhages
Potential complement activation	AE within SMQ: Hypersensitivity
Reduced thryroxine	AE within SMQ: Hypothyroidism

Results by type of haemorrhagic eventsmay be provided; the type of haemorhagic events and respective definitions will bespecified prior to database lock.

3.3.2.3 Local Cutaneous Reactions at Injection Site {LCRIS}

The following MedDRA preferred terms are determined by the Sponsor's Pharmacovigilance personnel to represent the local cutaneous reaction at the injection site:

- Injection site erythema
- Injection site swelling
- Injection site pruritus
- Injection site pain
- Injection site tenderness

Only events that start on the day of injection and persist for at least two days, i.e. event onset date on the day of injection and resolution date not on the day of injection or the day after the injection, will be included. Events with onset date on the day of injection and missing resolution date will also be included. AEs with partial or missing dates will be handled as follows. First establish whether the event is treatment emergent (Details ofTEAEdefinition see section 3.3.2.6 for TEAEoccurred during the OLEstudy and section 3.3.2.7 for TEAEfor overall including the parent study and OLE study). If yes, then establish if the preferred terms match the ones listed in the LCRISdefinition. If yes, check whether the event onset dates are within the specified time frame. If at this stage, onset date is

missing or partially missing, the event will be considered to have started within the required time frame.

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

Percentage of injections leading to local cutaneous reactions at the injection site will also be summarized. Percentage of injections leading to local cutaneous reactions will be calculated for each patient as (A/B)*100, where A is the number of injections with a local cutaneous reaction at the injection site, and B is the total number of injections.

3.3.2.4 Flu-Like Reactions

The following MedDRA preferred terms are determined by the Sponsor's Pharmacovigilance personnel to be the flu-like reactions:

- Influenza like illness
- Pyrexia (or Feeling hot or Body temperature increased) plus at least two of the following symptoms:
  - Chills
  - Myalgia
  - Arthralgia

Only events that start on the day of injection or the day after injection will be included. AEs with partial or missing dates will be handled as follows. First establish whether the event is treatment emergent (Details of TEAE definition see section 3.3.2.6 for TEAE occurred during the OLE study and section 3.3.2.7 for TEAE for overall including the parent study and OLE study). If yes, then establish if the preferred terms match the ones listed in the flu-like reactions definition. If yes, check whether the event onset dates are within the specified time frame. If at this stage, onset date is missing or partially missing, the event will be considered to have started within the required time frame.

The number and percentage of patients in each treatment group experiencing flu-like reactions will be tabulated.

The percentage of injections leading to flu-like reactions will also be summarized. The percentage of injections leading to flu-like reactions will be calculated for each patient as (A/B)*100, where A is the number of injections associated with a flu-like reaction, and B is the total number of injections.

3.3.2.5 Mortality

Death that occurs after the first dose of ISIS 420915 will be analyzed as follows:

Time from **Day 1 of ISIS 420915** to the date of death for LSS and time from **CS3 Study Day 1** to the date of death for SS will be summarized for the patients that met the criterion using the following descriptive statistics: mean, standard deviation, median, P25, P75, and minimum and maximum.

3.3.2.6 OLE Study Analysis of TEAEs

TEAEs which occur during the OLE study include TEAEs which first occurred or worsened on or after **CS3 Study Day 1**. Derivation is described in Section 3.3.2.

The following categories of AEs in the OLE study will be summarized by treatment group from the parent study: all TEAEs; TEAEs leading to early discontinuation from Study Drug or from the study; and serious adverse events. The percentage of patients reporting the adverse event will be summarized by MedDRA System Organ Class (SOC) and Preferred Term (PT), and will be sorted by SOC alphabetically and then by decreasing frequency of PT within SOC.

Summaries of drug related TEAEs, TEAEs by maximum severity, TEAEs grouped by duration of exposure to the Study Drug at the start of the event (< 6 months, ≥ 6 months to < 12 months, ≥ 12 months to < 24 months, ≥ 24 months to < 36 months, ≥ 36 months to < 48 months, ≥ 48 months to < 60, ≥ 60 months) and Number of dose at the start of event (<26, ≥ 26 to < 52, ≥ 52 to < 104, ≥ 104 to < 156, ≥ 156 to < 208, ≥ 208 to 260, ≥ 260) will also be provided. Duration of exposure and the number of doses is calculated from **CS3 Study Day 1** to the start date of event.

All TEAEs will be summarized for subgroups defined by the following variables:

- Age at parent study screening (<65 years and >=65 years),
- Sex (Female and Male),
- Race (White, non-White),
- Region (North America, Europe and South America /Australasia),
- CM-ECHO Set (Included and Not Included).

As well as stratification factors at randomization during the parent study, including

- V30M TTR mutation (Yes, No),
- previous treatment with Vyndaqel® or Diflunisal (Yes, No),
- Disease stage (Stage 1 and Stage 2).

Results will not be provided for a variable if the overwhelming majority of patients are within one level of the subgroup. Non-TEAEs reported will be flagged in the all AE listing.

TEAEs in the following categories will also be summarized in tables and listed separately:

- Adverse events of special interest (defined in section 3.3.2.1)
- Other adverse events of interest (defined in section 3.3.2.2)
- Local cutaneous reactions at injection site (defined in section 3.3.2.3)
- Flu-like reactions (defined in section 3.3.2.4)

Summary tables of the number and percentage of patients with these adverse events will be displayed split by AE category and treatment group received in the parent study.

Mortality defined in section 3.3.2.5 on SS will be summarized.

A plot of incidence rates and relative risks for common TEAEs, with an incidence of 5% or more, by treatment group assigned in the parent study will be provided.

Summary of non-serious common TEAEs, with an incidence of 5% or more, will be presented by Preferred Term.

Summary tables of the number and percentage of patients with drug related bleeding TEAEs will be presented by bleeding location and Preferred Term.

3.3.2.7 Longitudinal Safety Analysis of TEAEs

For this summary TEAEs are defined as those events which first occurred or worsened on or after first dose of ISIS in the parent study.

Adverse events summaries including data from the combined study periods of the parent and OLE studies will be provided for subjects in the LSS analysis population. These summaries will include all TEAEs which started on or after the first dose of ISIS 420915 in the parent study and before the day of the patient's last contact date. For subjects who enrolled in the OLE study, the last contact date would be the one obtained from the OLE study. For subjects who are not enrolled in the OLE study the last contact date would be the one obtained from the parent study. Note that AEs which started during the gap period between the completion of the parent study and the first dose of the OLE study and are not considered TEAEs in the OLE study will still be included in these summaries. In other words, it is possible that there will be events which are not considered parent study TEAEs or OLE study TEAEs, but will be counted towards this analysis.

These TEAEs will be summarized for subgroups defined by the following variables: Age at parent study screening (<65 years and >=65 years), Sex (Female and Male), Race, Region (North America, Europe and South America /Australasia), and CM-ECHO Set (Included and Not Included). Results will not be provided for a variable if the overwhelming majority of patients are within one level of the subgroup.

Summaries of drug related TEAEs, TEAEs by maximum severity, adverse events leading to early withdrawal from Study Drug, TEAEs duration of exposure to Study Drug at the start of event (< 6 months, ≥ 6 months to < 12 months, ≥ 12 months to < 24 months, ≥ 24 months to < 36 months, ≥ 36 months to < 48 months, ≥ 48 months to < 60 months, and ≥ 60 months)and Number of doses at the start of event (26, ≥ 26 to < 52, ≥ 52 to < 65, ≥ 65 to < 104, ≥ 104 to < 156, ≥ 156 to < 208, ≥ 208 to < 260, ≥ 260) will also be provided. Duration of exposure and the number of doses is calculated from **Day 1 of ISIS 420915** to the start date of event.

TEAEs in the following categories will also be summarized in tables and listed separately:

- Adverse events of special interest (defined in section 3.3.2.1)
- Other adverse events of interest (defined in section 3.3.2.2)
- Local cutaneous reactions at injection site (defined in section 3.3.2.3)
- Flu-like reactions (defined in section 3.3.2.4)

Summary tables of the number and percentage of patients with these adverse events will be displayed split by AE category.

Mortality defined in section 3.3.2.5 on LSS will be summarized.

3.3.3 Vital Signs, Weight, and Physical Examination Findings

Vital signs include systolic and diastolic blood pressure, pulse, respiratory rate, and temperature. Weight will also be analyzed. Absolute value at each visit, change and percent change from **ISIS 420915 baselines** to each visit in vital signs and weight will be summarized by treatment group of the parent study. Same summary for weight will also be presented based on the **parent study baseline** and the **OLE study baseline.** No statistical comparisons between treatments will be performed for this summary.

All vital signs and weight will be listed. Physical examination findings will also be listed.

3.3.4 Laboratory Measurements

Laboratory tests to ensure patient safety include chemistry panel, complete blood count with differential, thyroid panel, coagulation panel, immunogenicity, inflammatory panel, complement, and urinalysis. Absolute value, change and percent change from **ISIS 420915 baselines** will be summarized by visit and treatment group for continuous laboratory tests. No statistical comparisons between treatments will be conducted for these summaries. The mean value (and associated standard error) will be plotted by treatment group in the parent study or by V30M TTR mutation at randomization during the parent study over visits for the following laboratory parameters: platelets, creatinine clearance by CKD-EPI, Albumin, urine AC ratio, and urine PC ratio.

Summary for Albumin will also be presented based on the **parent study baseline** and the **OLE study baseline.**

All laboratory test results will be listed. Separate listings will be provided for local and central labs. The central lab listing will be based on the ADaM dataset and will include all central lab records. The local lab listing will be based on the SDTM dataset. A separate listing for platelets will be provided that includes assessment from both the local and central labs. A separate listing will contain only values outside of normal ranges. The number and percent of patients that stopped treatment because met a protocol-defined stopping rule for liver function, renal function, or platelet counts will be tabulated by treatment group of the parent study.

Additional investigation of hepatobiliary laboratory assessments, platelet counts and renal parameters will be performed, and are detailed in the sections below. In this investigation confirmed laboratory values will also be summarized.

A confirmed value is based on a consecutive lab value performed on a different day to, but within 7 days of, the initial value. If that value is in the same or worse category then 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.

3.3.4.1 Hepatobiliary Laboratory Abnormalities

The number and percentage of patients falling in each of the following categories based on all post-baseline assessments of the OLE study, including scheduled and unscheduled assessment on-study

period which spans the time drug is administered until the day of the patient's last contact date within the study, will be provided:

- ALT ≥ 3x Upper limit of normal (ULN) and total bilirubin ≥ 2xULN (with both events for any post-baseline results)
- Confirmed ALT ≥ 3x Upper limit of normal (ULN) and confirmed total bilirubin ≥ 2xULN (with both events for any post-baseline results)
- ALT ≥ 3xULN and international normalized ratio > 1.5 (with both events for post-baseline results)
- ALT ≥ 3xULN and total bilirubin ≥ 2xULN and ALP < 2xULN (with all three events for any post-baseline results)
- Hepatocellular injury
- Hepatocellular injury and total bilirubin ≥ 2xULN (with both events for any post-baseline results)
- ALT ≥ 3xULN
- ALT ≥ 5xULN
- ALT ≥ 8xULN
- ALT ≥ 10xULN
- ALT ≥ 20xULN
- Confirmed ALT ≥ 3xULN
- Confirmed ALT ≥ 5xULN
- Confirmed ALT ≥ 8xULN
- Confirmed ALT ≥ 10xULN
- Confirmed ALT ≥ 20xULN
- ALT ≥ 3xULN - < 5xULN
- ALT ≥ 5xULN - < 10xULN
- ALT ≥ 10xULN - < 20xULN
- Total bilirubin ≥ 2xULN
- ALP ≥ 2xULN and (**ISIS 420915 baseline** ALP < 2xULN or **ISIS 420915 baseline** ALP missing)
- ALT ≥ 3x ULN and ALT ≥ 2 x **ISIS 420915 baseline**
- Confirmed ALT ≥ 3x ULN and confirmed ALT ≥ 2 x **ISIS 420915 baseline**

For patients that had ALT elevation ≥ 3 xULN, the time from CS3 Study Day 1 to first ALT elevation ≥ 3 xULN will be summarized using the following descriptive statistics: mean, standard deviation, median, P25, P75, and minimum and maximum.

Shift tables from baseline for ALT, AST, and total bilirubin based on peak (maximum) and confirmed peak category will also be provided. Categories for the ALT and AST shift tables will be < 3 x ULN, ≥ 3 x ULN to < 5 x ULN, ≥ 5 x ULN to < 8 x ULN, and ≥ 8 x ULN. Categories for the total bilirubin shift table will be < 2 x ULN and ≥ 2 x ULN.

A hepatocellular injury event is defined as (ALT/ALT ULN)/(ALP/ALP ULN) ≥ 5 and ALT ≥ 3xULN, with the ALT and ALP assessments done on the same day.

The categories listed above will also be analyzed using AST instead of ALT. For these analyses the definition of hepatocellular injury will not be changed to depend on AST.

3.3.4.2 Platelets

The number and percentage of patients falling in each of the following categories (using available central and local laboratory assessments combined) based on post-baseline assessments, including scheduled and unscheduled assessment on-study period which spans the time drug is administered until the day of the patient's last contact date within the study, will be provided:

- Platelet count decrease - Grade 1a [≥ 100 10^9/L to < 140 x 10^9/L]
- Platelet count decrease - Grade 1b [≥ 75 10^9/L to < 100 x 10^9/L]
- Platelet count decrease - Grade 2 [[≥ 50 10^9/L to < 75 x 10^9/L]
- Platelet count decrease - Grade 3 [≥ 25 10^9/L to < 50 x 10^9/L]
- Platelet count decrease - Grade 4 [< 25 x 10^9/L]
- Confirmed Platelet count decrease - Grade 1a [≥ 100 10^9/L to < 140 x 10^9/L]
- Confirmed Platelet count decrease - Grade 1b [≥ 75 10^9/L to < 100 x 10^9/L]
- Confirmed Platelet count decrease - Grade 2 [[≥ 50 10^9/L to < 75 x 10^9/L]
- Confirmed Platelet count decrease - Grade 3 [≥ 25 10^9/L to < 50 x 10^9/L]
- Confirmed Platelet count decrease - Grade 4 [< 25 x 10^9/L]
- Maximum toxicity grade (Grade 1a , Grade 1b, Grade 2, Grade 3, Grade 4)
- Confirmed maximum toxicity grade (Grade 1a , Grade 1b, Grade 2, Grade 3, Grade 4)
- Value < 140 x 10^9/L
- Confirmed ≥ 30% decrease from the **ISIS 420915 baseline**
- Confirmed ≥ 50% decrease from the **ISIS 420915 baseline**
- Confirmed value < 140 x 10^9/L
- Confirmed value < 100 x 10^9/L
- Confirmed value < 75 x 10^9/L
- Confirmed value < 50 x 10^9/L
- Confirmed value < 25 x 10^9/L

Note that a platelet value of 140 x 10^9/L is the lower limit of normal for the central laboratory and will be used as the LLN for all platelet assessments. Furthermore, the platelet counts that define platelet count decrease grades are based on interactions with a regulatory authority, and align with the definitions from the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (except that the CTCAE does not subdivide Grade 1 into Grade 1a and 1b).

Shift tables from baseline will be provided using the nadir value and the confirmed nadir category. Categories for the shift table will be ≥ 140 x 10^9/L, ≥ 100 x 10^9/L to < 140 x 10^9/L, ≥ 75 x 10^9/L to < 100 x 10^9/L, ≥ 50 x 10^9/L to < 75 x 10^9/L, ≥ 25 x 10^9/L to < 50 x 10^9/L, and < 25 x 10^9/L.

Time from **CS3 Study Day 1** to the onset of each of these events collected in the OLE study will be summarized for the patients in SS that met the criterion. Summaries including the following descriptive statistics: mean, standard deviation, median, P25, P75, and minimum and maximum.

Kaplan-Meier plots for time to first event will also be provided for value < 140 x10^9/L, value < 100 x10^9/L and value < 75 x10^9/L .

The post-baseline nadir (absolute value, change from the **ISIS 420915 baseline**, and percent change from the **ISIS 420915 baseline**) of platelet count will be summarized by treatment group of the parent study.

Duration of platelet counts below the 140 x 10^9/L will be summarized, based on the duration (in weeks) each patient was below the 140 x 10^9/L.

The above analyses will be repeated for the subgroups defined by CM-ECHO Set.

Scatter plots for nadir platlets versus the **ISIS 420915 baseline** of BMI, mBMI, and weight will be provided.

A listing of patients with dose pause due to Platelet < 75 x10^9/L will also be provided.

3.3.4.3 Renal Parameters

The number and percentage of patients falling in each of the following categories (using available central laboratory assessments) based on post-baseline assessments, including scheduled and unscheduled assessment on-study period which spans the time drug is administered until the day of the patient's last contact date within the study, will be provided:

- Creatinine clearance by CKD-EPI < 90 mL/min/1.73m^2
- Creatinine clearance by CKD-EPI < 60 mL/min/1.73m^2
- Creatinine clearance by CKD-EPI < 30 mL/min/1.73m^2
- Creatinine clearance by CKD-EPI < 15 mL/min/1.73m^2
- Creatinine clearance by CKD-EPI ≥ 25% decrease from the **ISIS 420915 baseline**
- Creatinine clearance by CKD-EPI ≥ 50% decrease from the **ISIS 420915 baseline**
- Urine Alb/C ratio > 5 x ULN
- Urine P/C ratio > 5 x ULN
- Serum creatinine increase > 44.2 umol/l (0.5 mg/dL) from the **ISIS 420915 baseline**
- Confirmed creatinine clearance by CKD-EPI < 90 mL/min/1.73m^2
- Confirmed creatinine clearance by CKD-EPI < 60 mL/min/1.73m^2
- Confirmed creatinine clearance by CKD-EPI < 30 mL/min/1.73m^2
- Confirmed creatinine clearance by CKD-EPI < 15 mL/min/1.73m^2
- Confirmed creatinine clearance by CKD-EPI ≥ 25% decrease from the **ISIS 420915 baseline**
- Confirmed creatinine clearance by CKD-EPI ≥ 50% decrease from the **ISIS 420915 baseline**
- Confirmed urine Alb/C ratio > 5 x ULN
- Confirmed urine P/C ratio > 5 x ULN
- Confirmed serum creatinine increase > 44.2 umol/l (0.5 mg/dL) from the **ISIS 420915 baseline**

Shift tables from baseline for creatinine clearance by CKD-EPI will be provided using the nadir value and the confirmed nadir category. Categories for the shift table will be ≥ 90 mL/min/1.73m^2, ≥ 60

mL/min/1.73m^2 to < 90 mL/min/1.73m^2 , ≥ 30 mL/min/1.73m^2 to < 60 mL/min/1.73m^2 , ≥ 15 mL/min/1.73m^2 to < 30 mL/min/1.73m^2, and <15 mL/min/1.73m^2.

Shift tables from baseline for hemoglobin will be provided using the nadir value. Categories for the shift table will be Grade 0 (≥LLN, Absent), Grade 1 (< LLN - 100.0 g/L, Mild), Grade 2 (< 100.0 - 80.0 g/L, Moderate) and Grade 3 (< 80.0 g/L, Severe).

The above analyses will be repeated for the subgroups defined by CM-ECHO Set.

3.3.4.4 Longitudinal Safety Analysis of Laboratory Measurements

Laboratory measurements summaries including data from the combined study periods of the parent and OLE studies will be provided for subjects in the LSS analysis population. These summaries will include lab results specified in this section which occurred on or after the first dose of ISIS420915 in the parent study and before the day of the patient's last contact date. For subjects who enrolled in the OLE study, the last contact date would be the one obtained from the OLE study. For subjects who are not enrolled in the OLE study, the last contact date would be the one obtained from the parent study:

- Hepatobiliary laboratory abnormalities (defined in section 3.3.4.1);
- Platelets (defined in section 3.3.4.2);

  Note: For longitudinal safety analysis, Time to events will be started from **Day 1 of ISIS 420915** instead of **Study Day 1**.

- Renal parameters (defined in section 3.3.4.3)

Summaries for these abnormal lab test results will be provided for patients on active treatment in the parent study in LSS.

3.3.5 Electrocardiograms

Absolute value, change and percent change from the **ISIS 420915 baseline** in ventricular rate and ECG intervals (PR, QRS, QT, QT interval corrected for heart rate interval calculated using Fridericia's formula [QTcF], QT interval corrected for heart rate int erval calculated using Bazett's formula [QTcB]) will be presented by treatment group of the parent study and visit. Shift tables from the **ISIS 420915 baseline** to the worst (highest) post-baseline value by treatment group of the parent study will be used to assess the change in the QTcF interval. The categories for the shift table will be: ≤450 msec, >450 msec to ≤ 480 msec, >480 msec to ≤ 500 msec, and > 500 msec. The number and percent of patients experiencing an increase from baseline in QTcF interval of greater than 30 msec or 60 msec at any time post-baseline will be summarized by treatment group of the parent study. This analysis will be presented overall and also by the subgroup whose QTcF was normal at the **ISIS 420915 baseline**. Normal QTcF will be defined as ≤450 msec for males or ≤470 msec for females. The number and percent of patients with overall qualitative ECG abnormalities will also be summarized. These analyses will be repeated for patients in the CM-ECHO Set. No statistical comparisons between treatments will be performed for these summaries.

Ventricular rate and ECG intervals (PR, QRS, QT, QTcF, QTcB), as well as treatment-emergent abnormalities, will be listed. The number and percent of patients that stopped treatment because they met a protocol-defined stopping rule for QT interval corrected for heart rate prolongation will be tabulated by treatment group of the parent study. This tabulation will be repeated for patients in the CM-ECHO Set.

The ECG over-read data are used to support medical monitoring and will not be used for the ECG summary and analysis. A by-subject listing of ECG over-read data will be provided.

3.3.6 Electroretinograms (ERG) and Ophthalmology Exam

Change from the **ISIS 420915 baselines** in ERG results will be summarized by treatment group of the parent study.

ERG results will be listed. Ophthalmology exam findings will be listed. The number and percent of patients reaching protocol defined stopping rules for ocular effects will be tabulated by treatment group of the parent study.

3.4 Efficacy Analyses

All analyses and summaries by visits will be performed based on analysis visits defined in the section 3.2.1.3 "Analysis Visit Windows".

3.4.1 Descriptive Statistics

For all efficacy endpoints, descriptive summary statistics for absolute values, change or percent change from baseline, if applicable, will be provided by analysis visits for FAS and PPS.

For change or percent change from the **parent study baseline**, analysis visits are defined for Week 35 and Week 65 or 66, if applicable, from the parent study and for Week 26, Week 52, Week 78, Week 104, Week 130 and Week 156 in the OLE study. Analysis visits of Year 4 Week 52 and Year 5 Week 52 will also be included for NIS, Norfolk QOL-DN, SF-36 Questionnaire and PND Score.

For change or percent change from the **OLE study baseline**, analysis visits are defined for Week 26, Week 52, Week 78, Week 104, Week 130 and Week 156 in the OLE study. Analysis visits of Year 4 Week 52 and Year 5 Week 52 will also be included for NIS, Norfolk QOL-DN, SF-36 Questionnaire and PND Score.

By patient listings for all efficacy endpoints will be provided.

For the two primary endpoints (mNIS+7 score and Norfolk QOL-DN total score), data collected outside the analysis windows in the OLE study, e.g. before Week 26, Week 26 to Week 52, Week 52 to Week 78, Week 78 to Week 104, Week 104 to Week 130, Week 130 to Week 156, and after Week 156 will not be summarized. These data will be included in the listings.

For mNIS+7 score and Norfolk QOL-DN total score, descriptive statistics by subgroup and treatment groups of the parent study will also be provided for the following subgroups:

- Stratification factor: V30M TTR mutation (Yes, No)

- Age at the parent study screening (< 65 years old, ≥ 65 years old)
- Race (White, non-White)
- Sex (Male, Female)
- Region (North America, Europe, South America /Australasia)
- Previous treatment with Vyndaqel® or Diflunisal (Yes, No) prior to the parent study
- Disease stage at the parent study screening (Stage 1, Stage 2)
- CM-ECHO Set (Included, Not included)
- Through the whole OLE study, if the patient took any Vyndaqel® (Yes, No)

3.4.2 Efficacy Endpoints: mNIS+7 Score and Components, Norfolk QOL-DN Total Score and Domain Scores

The efficacy endpoints that are statistically analyzed are the following

- Change and percent change in the mNIS+7 score from either the **parent study baseline** or the **OLE study baseline** to Week 78 and Week 156
- Change in the Norfolk QOL-DN questionnaire total score from either the **parent study baseline** or the **OLE study baseline** to Week 78 and Week 156
- Change in the mNIS+7 components (NIS, heat-pain sensory, touch-pressure sensory, nerve conduction and heart rate to deep breathing tests) from either the **parent study baseline** or the **OLE study baseline** to Week 78 and Week 156
- Change in the Norfolk QOL-DN questionnaire domain scores (symptoms domain score for Stage 1 patients, and physical functioning/large fiber neuropathy domain score for Stage 2 patients) from either the **parent study baseline** or the **OLE study baseline** to Week 78 and Week 156

The maximum mNIS+7 composite score is 346.32 points. It can be broken into two components: the NIS component (maximum of 244 points) and the modified +7 component (maximum of 102.32 points). It can be further divided into the following 8 components: cranial nerves, muscle weakness, reflexes, sensory, heart rate deep breathing, nerve conduction, touch-pressure sensory, and heat-pain sensory.

The normal deviates (nds) from heart rate deep breathing and nerve conduction will be used in calculation of mNIS+7.

The mNIS+7 assessment is conducted at the parent study baseline (2 times), Week 35, 66 (2 times), the OLE study Week 26, 52, 78 (2 times), 104, 130 and 156 (2 times) visit. For visits where repeated assessments are done, the average will be used for analysis. Subcomponent scores will be averaged first, and the average composite score will be computed by summing the averaged subcomponent scores.

3.4.2.1 Additional Efficacy Analysis on the Change from the <u>Parent Study Baseline</u>

The following additional analysis will be done for mNIS+7 score and Norfolk QOL-DN total score:

- **Degree of Progression** – The degree of progression in the parent study and this OLE study will be summarized using the FAS. The degree of progression is defined as the change in the endpoint per one month. The degree of progression and corresponding 95% CI will be derived separately for each treatment group. A plot of degree of progression over time by treatment group assigned in the parent study will also be provided. The degree of progression will be derived over the 15 months treatment period of the parent study and then over 12 months treatment intervals in the OLE study. The degree of progression will be summariezed described in section 3.4.1as follows:
    - Average monthly progression over the first 15 months (i.e. from the first dose administered to Week 66 in the parent study) will be derived by dividing the estimated change from parent study baseline to Week 66 by 15.
    - Average monthly progression over the first 12 month interval in the OLE study will be estimated by dividing the estimated change from Week 66 in the parent study to Week 52 in this OLE study by 12.
    - Average monthly progression over the second 12 month interval in the OLE study will be estimated by dividing the estimated change from Weeks 52 to Week 104 in this OLE by 12.
    - Average monthly progression over the third 12 month interval in the OLE study will be estimated by dividing the estimated change from Weeks 104 to Week 156 in this OLE by 12.

- **Responder Analysis for mNIS+7 score** – A responder analysis based on the change in mNIS +7 score will be conducted to examine whether improvement in response is consistent over a range of response thresholds using the OLE study FAS. A responders is defined as a patient whose mNIS +7 score change from the **parent study baseline** to the respective post-baseline visit in the OLE study, i.e. Weeks 26, 52, 78, 104, 130, 156 from the OLE study, is less than or equal to the threshold value. Threshold values to be tested will include 0, 2, 4, 6, 8, 10, 15, 20, 30 points above the baseline values. For each response threshold, the response rates at each post-baseline visit in the OLE study for both the treated group and the placebo group will be calculated and plotted against the response threshold. Evaluable patients that terminate treatment early irrespective of the reason or had missing the respective post-baseline visit in the OLE study data will be considered a non-responder. Because a patient may not be followed in the OLE long enough to contribute data at a visit, the analysis at a visit is limited to evaluable patients, defined as patients who are in the study longer than the upper bound of analysis visit window for that visit (see Table 1 of Appendix 3 Analysis Visit Windows). For example, the week 26 window extends up to day 206, and a patient would be considered evaluable at Week 26 if (data cut date – first dose date) was more than 206 days.

The efficacy analyses described in this section will be repeated using the OLE study PPS.

3.4.2.2 Additional Efficacy Analysis on the Change from the OLE Study baseline

The following additional analysis will be done for mNIS+7 score:

- **Responder Analysis for mNIS+7 score** described in section 3.4.2.1 based on the change in mNIS +7 score from the **OLE study baseline** will be performed.

The efficacy analyses described in this section will be repeated using the OLE study PPS.

3.4.3 Other Efficacy Endpoints

Descriptive statistics, as described in section 3.4.1 (but without stratification by subgroup) will also be provided for the following efficacy endpoints:

- Change and percent change in mBMI and BMI from either the **parent study baseline** or the **OLE study baseline** to Week 78 and Week 156 in the FAS and PPS
- Shift table from either the **parent study baseline** or the **OLE study baseline** in PND score from to Week 78 and Week 156 in the FAS and PPS
- Change and percent change from either the **parent study baseline** or the **OLE study baseline** in NT-proBNP in the FAS, PPS, ECHO subgroup and CM-ECHO Set. Change in log-transformed NT-proBNP from either the **parent study baseline** or the **OLE study baseline** to Week 78 and Week 156 in the FAS, PPS, ECHO subgroup and in the CM-ECHO Set
- Change and percent change in the SF-36 questionnaire domain scores, including Physical Component Summary Score, Mental Component Summary Score, and Mental Health Domain Score from either the **parent study baseline** or the **OLE study baseline** to Week 78 and Week 156 in the FAS and PPS
- Change and percent change from either the **parent study baseline** or the **OLE study baseline** to Week 78 and Week 156 in NSC in the FAS and PPS
- Change and percent change from either the **parent study baseline** or the **OLE study baseline** to Week 78 and Week 156 in the NSC individual domain scores (muscle weakness, sensory [hypo/loss of sensation], sensory [paresthesia, hyper sensation], autonomic [GI/urinary incontinence], and autonomic [other than GI//urinary incontinence]) in the FAS and PPS.

Analysis for ECHO will be included in a separate SAP for the following endpoints:

- Change and percent change in GLS by ECHO from either the **parent study baseline** or the **OLE study baseline** to Week 78 and Week 156 in the parent study ECHO subgroup, OLE ECHO set and in the Cardiomyopathy-ECHO (CM-ECHO) Set
- Change and percent change in the ECHO parameters (except GLS) in the parent study ECHO subgroup, OLE ECHO set and in the CM-ECHO Set from either the **parent study baseline** or the **OLE study baseline** to Week 78 and Week 156

Note that the 7 point change score (-3, -2, -1, 0, 1, 2, 3) that is recorded on the NSC questionnaire will be listed but not summarized or analyzed. Similarly for questions 20-29 the location is only listed. Questions 31-34 are of particular interest and therefore the number and percentage of patients responding 0 (No), 1 (slight +), 2 (moderate ++) or 3 (severe +++) will be presented.

3.5 Pharmacodynamic (PD) Analyses

Descriptive statistics as described in section 3.4.1 (but without stratification by subgroup) will also be provided the following PD endpoints:

- Change and percent change in TTR level from either the **parent study baseline** or the **OLE study baseline** to Week 78 and Week 156
- Change and percent change in RBP4 level from either the **parent study baseline** or the **OLE study baseline** to Week 78 and Week 156.

In addition the proportion of patients with percentage decrease from either the **parent study baseline** or the **OLE study baseline** in plasma transthyretin (TTR)≥60% will be summarized by parent study treatment group at each visit.

As not all subjects will get to year 4 and 5 of the study, data from year 4 and 5 will be summarized as described in section 3.4.1.

3.6 Pharmacokinetic (PK) and Immunogenicity (IM) Analyses

PK endpoints include the following:

- Plasma trough and post-treatment levels of ISIS 420915 in all evaluable patients in the OLE study PK set

IM endpoints include the following:

- IM status [confirmed positive/negative or unevaluable and, when applicable, titer of anti-ISIS 420915 antibodies (ADA)] in all patients in the OLE study SS
- IM status (positive, negative or 'unknown') and its characteristics if applicable (onset, duration, peak titer, time to reach peak titer, etc.) in the OLE study SS

Plasma samples will be collected at protocol designated times for ISIS 420915 plasma PK and IM assessments.

3.6.1 Plasma Pharmacokinetics

Plasma concentrations of ISIS 420915 will be summarized at interim analyses and final analysis at EOS of the OLE study.

Plasma concentrations of ISIS 420915, along with the scheduled (nominal) and actual sampling times (i.e., time from subcutaneous dosing) will be listed for each evaluable patient by treatment group of the parent study, actual dose, gender, patient immunogenicity (IM) status, and study day. Plasma concentrations below the lower limit of quantification (LLOQ) will be indicated by "BLQ". Percent differences between nominal and actual dose, as well as between scheduled and actual sampling times will also be listed for all patients.

ISIS 420915 plasma trough (predose) concentrations will be summarized using descriptive statistics by dose, study day, and scheduled time point, without and with stratification by prior treatment in the parent study and patient IM status (see Section 3.6.2). For the purpose of calculating typical summary descriptive statistics (n, mean, SD, %CV, geometric mean, geometric %CV, percentiles (e.g., median, P25, and P75), minimum, and maximum) for plasma concentrations, all BLQ values will be set to zero. Mean plasma concentrations that are below the LLOQ will be presented as BLQ, and the SD, SE, and %CV will be reported as not applicable. Other stratifications may also be

performed if deemed warranted to properly interpret the pharmacokinetic analysis. Samples will be excluded from descriptive statistics if there are large deviations between scheduled and actual sampling times (percent difference between scheduled and actual sampling time greater than 30%), or large deviations between actual dose and nominal dose (percent difference between nominal and actual dose greater than 30%). Any samples excluded from the summary descriptive statistics, if deemed necessary, will be listed separately along with the reason for exclusion.

For all evaluable patients, ISIS 420915 plasma trough (predose) concentrations versus time (actual) profiles for each individual patient, as well as corresponding mean (±SD) plasma concentration versus time (scheduled) profiles will be presented graphically on linear and semilogarithmic scales, without and with stratification by prior treatment in the parent study and patient immunogenicity status (see Section 3.6.2). Other stratifications may also be performed if deemed warranted. At the discretion of the pharmacokineticist and/or biostatistician, samples may be excluded from the mean plots if there are large deviations between scheduled and actual sampling times, or large deviations between actual dose and nominal dose.

3.6.2 Immunogenicity (IM) Analyses

Samples collected during treatment and post-treatment period, including early termination and unscheduled samples for IM assessment as specified in the study protocol will be analyzed for ADA. However, plasma samples collected at other time points (or for PK purposes) may also be potentially evaluated if deemed of further interest and warranted by the pharmacokinetic scientist. Samples that are confirmed IM positive are subjected for titering, which may include but not limited to the samples collected on Days 85, 176, 358, 540, 722, or 1086 during treatment period.

An evaluable sample will be designated 'IM positive' based on both positive screening and confirmation assay results (i.e., confirmed positive result); otherwise, the sample will be deemed 'IM negative'. Sample IM results (screen positive/negative, confirmed positive/negative or unevaluable, and when applicable, titer of anti-ISIS 420915 antibodies) during and after treatment with study drug (ISIS 420915) (sample IM status) will be listed by the subject's prior treatment in the parent study, dose, and study day.

Patient IM status: Study patients will be given 'IM positive' status if they have at least one confirmed positive sample result at any time during the treatment or post-treatment evaluation periods. Study patients will be given 'IM negative' status if all evaluated IM sample results during the treatment and post-treatment evaluation periods are IM negative and they have at least one evaluable IM result collected post study drug treatment. Otherwise, a study patient will be given 'unknown' IM status. Subject IM results will be listed by treatment group of the parent study and dose for all evaluable patients, which will include but may not be limited to: patient IM status (positive, negative or unknown), the day associated with the first positive IM status emerged since receiving ISIS 420915 treatment (T_{first}, i.e., onset of ADA development as described below), the last positive IM status observed (T_{last}), the last evaluable IM sample collected ($T_{last\ sampling}$), peak titer, and time to reach peak titer.

Onset of immunogenicity: The onset (T_{first}) of anti-ISIS 420915 antibodies for OLE study will be derived as the difference between the date when first immunogenicity sample becomes confirmed positive (i.e., positive sample IM status) and Day 1 of ISIS 420915 plus one.

- If a patient has confirmed positive IM samples detected on or prior to Day 1 of ISIS 420915, e.g., pre-existing antibodies cross-react with ISIS 420915, the onset in the OLE study for that patient would be less or equal to 0 (≤ 0).

Other immunogenicity data analysis (e.g. classification as persistent or transient status, etc.) may be performed as described below (Shankar et al, 2014) if deemed warranted at the discretion of the pharmacokineticist, medical monitor, and/or biostatistician.

Transient ADA response will be defined as:

– 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 ought to 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 will be defined as:

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

The sample IM incidence (number) and incidence rate (percent) at each evaluated study time point, and for the overall treatment and post-treatment evaluation period, as well as subject IM incidence and incidence rate, will be determined and appropriately summarized by treatment group of the parent study, as the total number of and percentage of evaluated subjects with IM negative, positive, and unknown status. Subjects with positive IM status may further be classified as transient or persistent status if applicable, with incidence and incidence rate being transient or persistent appropriately summarized. Furthermore, onset, titer over time, peak titer of the ADA response, and time to reach peak titer, if applicable, will be also appropriately summarized (using descriptive statistics) as median, quartiles (25% and 75%), and range and presented graphically, if deemed appropriate, by treatment group of the parent study (e.g., summarized at each evaluated study time point and overall; summarized by observed peak titer values from the individual IM positive patients; etc.).

- Onset in days = The date of first sample has "positive" sample IM status - **Day 1 of ISIS 420915** +1;
- Time to reach peak titer in days = The date of peak titer observed- **Day 1 of ISIS 420915** +1;

In addition to PK assessments (Section 3.6.1), selected efficacy (Sections 3.4 to 3.5) and safety (Section 3.3) assessments will also be further stratified by patient IM status (i.e., patient IM status being positive, negative, or unknown) and presented in tables and/or graphically, as deemed appropriate or warranted by the designated study pharmacokineticist, medical monitor, and/or biostatistician. Efficacy measures to be stratified by patient IM status will include, but may not be limited to, TTR level, mNIS+7, and Norfolk QOL-DN score. Safety measures to be stratified by patient IM status will include, but may not be limited to, AEs, and lab tests for hematology and kidney functions.

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.

4. Sample Size

No sample size calculations were performed as this is an extension study to the double-blind, placebo-controlled ISIS 420915-CS2 study. Approximately 135 patients were planned to be eligible to enroll into this present OLE study.

5. Interim Analyses

Database closing and locking will be done at the following milestones:

1. When all patients in the parent study have completed the EOT assessments, the OLE study database will be cleaned and will be unblinded according to CS2 unblinding plan. Therefore, all treatment information is available for this OLE study to the team specified in the CS2 unblinding plan. This interim analysis will be used to support the FAP regulatory file. For this interim analysis the data cut-off date utilized was prior to the last subject completing EOT assessments in the parent study CS2 to allow sufficient time for data cleaning prior to closing the database for analysis.
2. After all patients complete the study (at EOS). This will be considered the final analysis of this OLE study.

Additional closing and locking may be done to support additional interim analyses, with the timing of the database closing and locking coinciding with regulatory requirements or study milestones.

5.1 Interim Analysis at EOT of the Parent Study

A planned interim analysis of the OLE study based on cleaned database will be performed after all patients in the parent study have completed EOT assessments and the parent study is unblinded according to CS2 unblinded plan.

The following will not be performed as part of this interim analysis:

- Summaries using PPS
- The review of protocol deviations to identify those leading to exclusion from the PPS

The table below lists what data will be included in the summary output by endpoint type and what output is planned for this interim analysis at the parent study EOT.

Provided at interim of OLE study (at parent study EOT)	Comment
Patient Characteristics	
• Summaries of patient disposition, protocol deviations, analysis sets.	- For all enrolled patients
• Summary of demographic characteristics and baseline characteristics and exposure to Study Drug.	- For SS
• Concomitant medication.	- On-study summary for SS
• The longitudinal safety analysis of exposure to Study Drug.	- For LSS
• Corresponding listings.	
Efficacy and PD	
• By visit summary table for each endpoint, Include summary statistics (absolute, change and/or percent change from baselines) based on both the **parent study baseline** and the **OLE study baseline.**	- On-treatment summary for FAS
• Boxplot of Absolute Value, Change from Baseline, and/or Percent Change from Baseline over Time based on both the **parent study baseline** and the **OLE study baseline.**	- On-treatment summary for FAS - Only plot time points where at least 20% of the CS3 population have data
• Summary table and figure for Response Rate byThreshold Value by Visit.	- On-treatment summary for FAS
• Corresponding listings.	- All results collected in CS3 before IA data cut
Safety Endpoint	
• Summary tables for AE.	- On-Treatment and On-Study for SS
• Summary tables of safety lab, vital sign, ECG, ERG by visit.	- On-Treatment+ Post-Treatment for SS
• Summary table and shift table of abnormal safety lab results, ECG worst values and stopping rules.	- Abnormal safety lab is on-study for SS
• The longitudinal safety analysis of AE and abnormal safety lab results, including hepatobiliary, platelets and renal parameters.	- For LSS
• Corresponding listings.	- All results collected in CS3 before IA data cut
lmmunogenicity	

Provided at interim of OLE study (at parent study EOT)	Comment
• Summary table for sample **IM** status, anti-ISIS 420915 antibody titer values, patient IM status, onset and peak titer of the ADA, time to reach peak titer. • Box Plot of Titer over Time.	- On-study summary for SS
• mNIS+7, Norfolk total score and TTR summary by patient IM status. • Box plot for mNIS+7 and Norfolk totalscore by patient IM status.	- Efficacy is on-treatment for FAS - Patient IM status ison-study for SS
• Summary table of AE by patient IM status.	- AE is on-treatment and On-Study for SS - Patient IM status is on-study for SS
• Summary table and shift table of abnormal safety lab results by patient IM status.	- Abnormal safety lab is on-study for SS - Patient IM status ison-study for SS
• Corresponding listings.	- All results collected in CS3 before IA data cut
PK	
• Summary table of ISIS 420915 Trough Plasma Concentrations (ng/mL) with and without Stratification by prior treatment in the parent study and Subject lmmunogenicity Status	- On-study for PK set
• Figure of Mean (±SD) of ISIS 420915 Plasma Trough Concentrations (ng/mL) over Time by prior treatment in the parent study and Subject lmmunogenicityStatus	- On-study for PK set - plot time points where at least 20% of the CS3 population have data
• Corresponding listings	- All results collected in CS3 before IA data cut

5.2 Interim Analysis for Day-90 Updates

The CS3 safety results for 90-day safety update are based on the data as of the data cutoff date of 15-Sep-2017. lmmunogenicity results are based on a data cutoff date of 08-Jul-2017 due to timing of sample collection, batch sizes, and processing schedules. The following data were included in the interim analyses: dispositions, demographics, concomitant medications, exposure, adverse events (AEs), laboratory results, vital signs, physical examinations, electrocardiograms (ECGs), electroretinograms (ERGs), and immunogenicity {IM).

The following will not be performed as part of this interim analysis:

- Summaries using PPS, FAS, ECHO subgroup, OLEECHO set and Longitudinal analysis set

- The review of protocol deviations to identify those leading to exclusion from the PPS
- Descriptive summary for efficacy and PD endpoints

In addition, listings will be provided for patients who will be found with following conditions after Feb. 28th 2017. A note: Feb. 28th 2017 is the data cut for supporting CS2 EOT submission:

- Platelet count <100 X 10"9/L;
- Platelet count confirmed value <100 X 10"9/L;
- Confirmed Nadir Creatinine Clearance by CKD-EPI (ml/min/1.73m2) shift from **ISIS 420915 Baseline** to category 2 or above;
- Confirmed nadir creatinine clearance by CKD-EPI decreasing 25% from **ISIS 420915 Baseline** or more in which percent change= (post-baseline - baseline)/baseline;
- Confirmed nadir creatinine clearance by CKD-EPI decreasing 50% from **ISIS 420915 Baseline** or more in which percent change= (post-baseline - baseline)/baseline.

The table below lists what data will be included in the summary output by endpoint type and what output isplanned for this interim analysis for Day-90 updates.

Provided at interim of OLE study (Day-90 updates)	**Comment**
Patient Characteristics	
• Summaries of patient disposition, protocol deviations, analysis sets.	- For all enrolled patients
• Summary of demographic characteristics and baseline characteristics (excluding efficiacy endpoints) and exposure to Study Drug.	- For SS
• Concomitant medication.	- On-study summary for SS
• Corresponding listings.	
Safety Endpoint	
• Summary tables for AE.	- On-Study for SS
• Summary tables of safety lab, vital sign, ECG, ERG by visit.	- On-Treatment+ Post-Treatment for SS
• Summary table and shift table of abnormal safety lab results, ECG worst values and stopping rules.	- Abnormal safety lab is on-study for SS
• Corresponding listings.	- All results collected in CS3 before IA data cut
lmmunogenicity	
• Summary table for sample IM status, anti-lSIS 420915 antibody titer values, patient IM status, onset and peak titer of the ADA, time to reach peak titer. • Box Plot of Titer over Time.	- On-study summary for SS

Provided at interim of OLE study (Day-90 updates)	Comment
• Summary table of AE by patient IM status.	- AE is On-Study for SS - Patient IM status ison-study for SS
• Summary table and shift table of abnormal safety lab results by patient IM status.	- Abnormal safety lab is on-study for SS - Patient IM status ison-study for SS
• Corresponding listings.	- All results collected in CS3 before IA data cut
PK	
• Summary table of (SIS 420915 Trough Plasma Concentrations (ng/ml) with and without Stratification by Subject lmmunogenicity Status	- On-study for PK set
• Figure of Mean (±SD) of (SIS 420915 Plasma Trough Concentrations (ng/ml) over Time Subject lmmunogenicity Status	- On-study for PK set - plot time points where at least 20% of the CS3 population have data
• Corresponding listings	- All results collected in CS3 before IA data cut

5.3 Interim Analysis II

CS3 Initerim analysis II are based on the data as of the data cutoff date of 31-MAY-2018. The following data were included in the interim analyses: dispositions, demographics, concomitant medications, exposure, adverse events (AEs), laboratory results, ECHO, mNIS+7, NIS, NIS-LL, Norfolk SF36, and PND score.

The table below lists what data will be included in the summary output by endpoint type and what output is planned for this interim analysis II.

Provided at interim II	Comment
Patient Characteristics (for CS3 and ISS)	
• Summary of demographic characteristics and baseline characteristics (excluding efficiacy endpoints) and exposure to Study Drug.	- For SS
• Concomitant medication.	- On-study summary for SS
• Listings for exposure, dropouts and dose pause	

Provided at interim II	Comment
Safety Endpoint (for CS3 and ISS)	
• Summary tables for AE.	- On-Study for SS
• Summary tables of safety lab (Hematology, Chemistry) by visit.	- On-Treatment+ Post-Treatment for SS
• Summary table and shift table of abnormal safety lab results and stopping rules.	- Abnormal safety lab is on-study for SS
• Survival plot for time from first ISIS dose to death or discontinuation	- On-Study for SS
• Listing of adverse events and medication occurred or took 30 days prior to platelet value <50x10^9/L	
• Listing of platelet values and anticoagulants or antiplatelets medication for subjects **with** grade 3 thrombocytopenia	
Efficacy (for CS3)	
• Summary table of mNIS+7, NIS, NIS-LL, SF-36 and PND score, NT-proBNP and Log-Transformed NT-proBNP	- On-treatment for FAS
• Listing of NSC domain, subdomain and totalscore	- CS3 Enrolled Patients
PD Parameters (for CS3)	
• Summary of TTR and RBP4 by visit.	- On-treatment for FAS
ECHO (for CS3)	
• Global Longitudinal Strain and Global Left Ventricular Size and Function - LV Mass	- On-treatment for Enrolled Patients and CM-ECHO Set

Interim II also create Topline efficacy/safety tables by subgroup/subset for CS3 (both efficacy and safety outputs) and ISS (safety outputs). The subgroup/subset are:

- Stage 3 patients (PND score=V at BL)
- V30M TTR Mutation (IVRS)
- Disease Stage (IVRS)
- Previous Treatment (IVRS)
- CM-ECHO Set

- NT-proBNP>650 pg/nL at BL
- NYHA 1 vs 2 at BL
- IVS>15 mm at BL
- Paitents who Diagnosed as TTR Cardiomyopathy at BL
- Efficacy of patients who had pauses vs those who didn't
- Patients who had pauses vs those who didn't (for primary endpoints only)
- Patients on lower dose which is subjects with dose <=150 for more than 12 weeks in CS2 and CS3 (for primary endpoints only)

6. Study Conduct to Minimize Bias

The sponsor recognizes the importance of confidentiality of interim results before the parent study is unblinded. To minimize any potential risk to the integrity of the study, the first interim analysis will be conducted only after the database of the parent study is locked and unblinded.

The ISIS 420915 CS2/CS3 DSMB will conduct regular safety reviews throughout the study. Until the parent study is unblinded, the outputs will be prepared by an independent statistician who is independent from the sponsor.

The independent statistician who supports DSMB will be an employee of a CRO (InVentiv), one that is independent from a second CRO conducting the trial (ICON) and a third CRO (PAREXEL) who will be performing the final statistical analysis. InVentiv will also provide programming support for the DSMB, handle all DSMB related analyses, independent of the Sponsor and independent of ICON and PAREXEL. The independent statistician from InVentiv will maintain secure custody of blinded and unblinded data to ensure the integrity of the data. Additionally, the independent statistician will maintain all unblinded data in electronic form in a secure area. All transfer of data/reports by the independent statistician to the DSMB, which includes patient data will be by secure, trackable courier and/or secure electronic means. The independent statistician will provide all of the unblinded data to the DSMB as outlined in the DSMB Charter.

All DSMB members will sign a Confidentiality Agreement with the Sponsor. In addition, all DSMB members will treat as confidential the reports, meeting discussions, minutes and recommendations of the DSMB. Strict rules for DSMB communication with the Sponsor have been put in place for the purpose of minimizing the potential for bias, as outlined in the DSMB Charter. All written communication described in the DSMB Charter will be by secure, trackable courier and/or secure electronic means. This includes dissemination of DSMB recommendations, and review of minutes of open and closed sessions between the DSMB and, as appropriate, other DSMB members and/or, the Sponsor contacts (primary, CMO and statistics).

During the conduct of this OLE study and before unblinding of the parent study, the Sponsor will not have access to any efficacy, PD or exploratory data, except for parent study baseline values and data collected after the Week 13 visit for the following endpoints: plasma retinol, plasma TTR, plasma RBP4 and plasma NT-proBNP . The efficacy data will be collected and stored by independent CROs as detailed below. All CROs will maintain secure custody of their databases. The CROs will not transfer any efficacy data other than baseline data or post-Week 13 data for certain endpoints to the Sponsor until after all patients in the parent study have completed the treatment period and the database of the parent study has been locked and unblinded. The efficacy or PD data includes the following: mNIS+7, NIS+7, Norfolk QOL-DN, BMI/mBMI, plasma retinol, plasma retinyl palmitate, plasma TTR, plasma RBP4, plasma NT-proBNP, SF-36 questionnaire, ECHO efficacy parameters, NSC and PND scores. Derived mNIS+7 and the components including NIS, +7 and modified +7, as well as NSC, Norfolk QOL-DN, PND, body weight and ECHO will be available before the parent study is unblinded to PAREXEL who are preparing this SAP and are performing statistical analysis.

For the purpose of data cleaning, an independent data manager at Trennic Data Services will also have access to post-baseline data for the following endpoints: mNIS+7, NIS+7, Norfolk QOL-DN, BMI/mBMI, SF-36 questionnaire, ECHO efficacy parameters, NSC and PND scores.

The primary efficacy assessment, mNIS+7 scores, will be collected and stored by an independent contract research group, Mayo Clinic Polyneuropathy Quality Assurance Core Facility (MC Core) that is under the direction of Dr. [redacted]. The NSC score is obtained during the NIS assessment procedure and is also collected and stored by MC Core. The mNIS+7 results from each site will be faxed to MC Core for processing and quality assurance. Faxed copies will be maintained in secure rooms within locked cabinets. The NIS and NSC data are stored in the RedCap (a database). The other components of the mNIS+7 (nerve conduction, sensory testing and heart rate to deep breathing) are entered by the MC Core into a firewalled portion of the study EDC system. MC Core only has access to this portion of the EDC system and the Sponsor and clinical sites do not have access to the MC Core portion of the EDC. The mNIS+7 summated score will not be shared with the sites. Up until the parent study database lock, the Sponsor will only have access to patient baseline values of the mNIS+7. Post-baseline values will be available for PAREXEL who are preparing this SAP and are performing statistical analysis.

The Norfolk QOL-DN, body weight (needed to calculate BMI/mBMI), SF-36 questionnaire and PND scores will be entered into the EDC system by each site. The independent CRO BioClinica is contracted to develop and maintain secure custody of the EDC database. During the conduct of this OLE study before unblinding of the parent study the Sponsor will receive regular data transfers from BioClinica but without the above mentioned efficacy data included (except for baseline values). Post-baseline values for most endpoints mentioned above except for SF-36 derived scores will be available for PAREXEL who are preparing this SAP and are performing statistical analysis.

The plasma retinol, plasma TTR, plasma RBP4, and plasma NT-proBNP samples will be assayed at Medpace, the central laboratory contracted for this study. The results will be maintained in Medpace's secure database. Neither the Sponsor nor the sites will receive the results from the above mentioned tests (except for baseline values) prior to week 13. During the conduct of this OLE study before unblinding of the parent study the Sponsor will receive regular lab data transfers from Medpace to perform safety assessments. The above mentioned data collected prior to Week 13 will not be available to PAREXEL or the sponsor.

The ECHO data will be collected, analyzed and stored in a secure database by CICL. The sites will upload the ECHO data on a secure web-portal for analysis by CICL. Up until the parent study database lock, the Sponsor will only have access to patient baseline ECHO values. ECHOs conducted for safety assessment purposes will be available to the DSMB, Sponsor, and Investigator. Post-baseline ECHO data will be available for PAREXEL who are preparing this SAP and are performing statistical analysis.

Prior to the parent study unblinding, any ISIS 420915 concentration data sets and IM data sets provided to Ionis Pharmaceuticals, Inc. by the respective bioanalytical labs will not include results for samples collected prior to Week 13, nor will they include results for unscheduled or early term (ET) samples to prevent the potential unblinding of the parent study.

In conclusion, the unblinding process before the parent study unblinding for periodic safety reviews has been clearly defined and detailed roles and responsibilities to the independent statistician, DSMB, Partner Firewalled Staff and Sponsor, such that the potential for bias to enter into the conduct of the study will be minimized. Additional steps to ensure the data for the primary and secondary endpoints remain blinded, such as housing the primary and secondary efficacy data in databases to which the Sponsor has no access, further safeguards the potential for Sponsor bias.

7. References

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Ionis document: QOL-DN Scoring Manual--updated 2006.pdf

Ionis document: mNIS+7_Quality_Manual_Version 2_final_03Sept2014.pdf

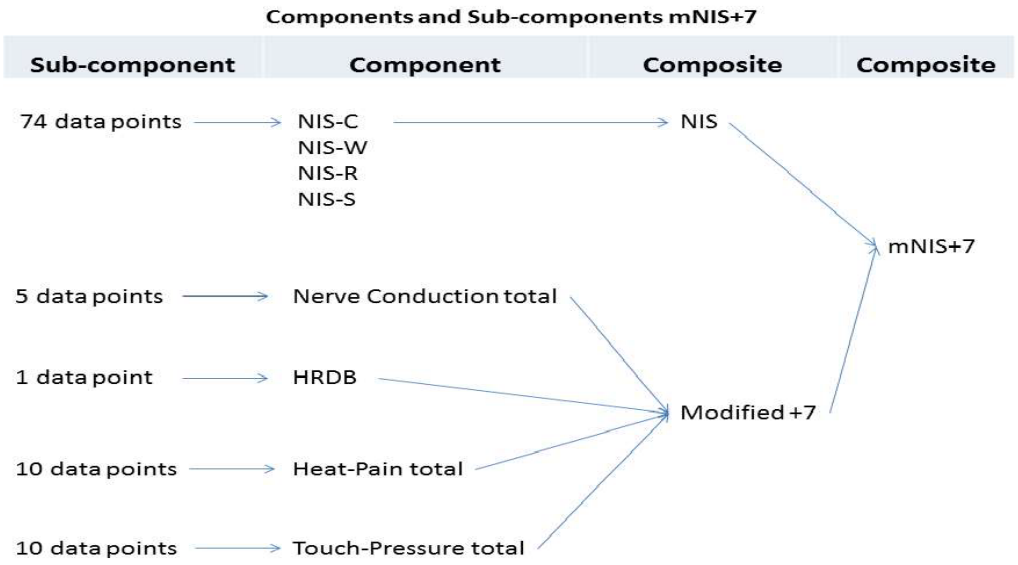
Ionis document: SF36-detailed score.pdf

Ionis document: 420915 CS2 unblinding plan

8. Appendices

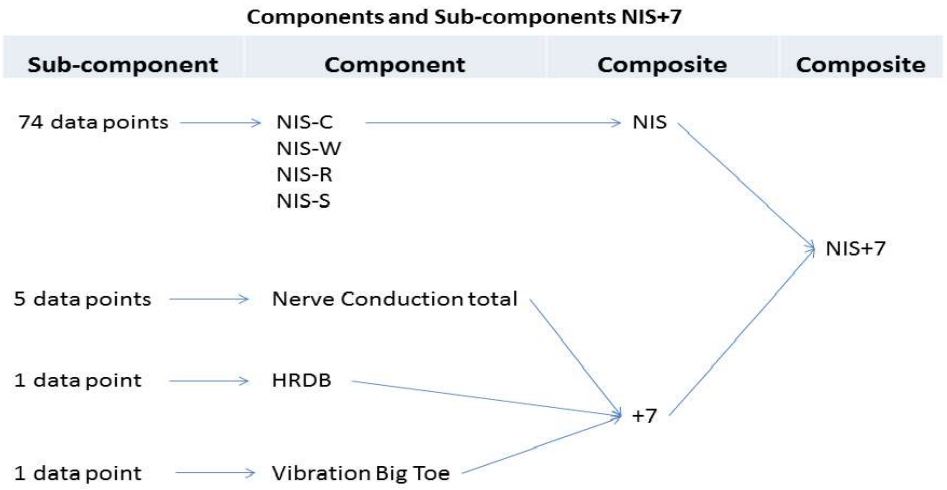
8.1 Appendix 1 Components and Subcomponents of the mNIS+7, and NIS+7

Figure 1 Components and Subcomponents of the mNIS+7



Note that only two of the five subcomponents for Nerve Conduction Total are shared in modified + 7 and + 7, which are fibular CMAP amplitude and sural SNAP amplitude.

Figure 2 Components and Subcomponents of the NIS+7



Note that only two of the five subcomponents for Nerve Conduction Total are shared in modified + 7 and + 7, which are fibular CMAP amplitude and sural SNAP amplitude.

Table 1: Neuropathy Impairment Score

Component	Assessment	Right Side	Left Side	Max Score	Max Sub-Totals	Missing value imputation for Component Score
Cranial Nerves (NIS-C)	1. 3rd Nerve	0-4	0-4	8		Group A
	2. 6th Nerve	0-4	0-4	8		
	3. Facial weakness	0-4	0-4	8		
	4. Palate weakness	0-4	0-4	8		
	5. Tongue weakness	0-4	0-4	8	40	
Muscle Weakness (NIS-W)	6. Respiratory	0-4	0-4	8		Group A
	7. Neck flexion	0-4	0-4	8		
	8. Shoulder abduction	0-4	0-4	8		
	9. Elbow flexion	0-4	0-4	8		
	10. Brachioradialis	0-4	0-4	8		
	11. Elbow extension	0-4	0-4	8		
	12. Wrist flexion	0-4	0-4	8		
	13. Wrist extension	0-4	0-4	8		
	14. Finger flexion	0-4	0-4	8		
	15. Finger spread	0-4	0-4	8		
	16. Thumb abduction	0-4	0-4	8		
	17. Hip flexion	0-4	0-4	8		
	18. Hip extension	0-4	0-4	8		
	19. Knee flexion	0-4	0-4	8		
	20. Knee extension	0-4	0-4	8		
	21. Ankle dorsiflexors	0-4	0-4	8		
	22. Ankle plantar flexors	0-4	0-4	8		
	23. Toe extensors	0-4	0-4	8	152	

Component	Assessment	Right Side	Left Side	Max Score	Max Sub-Totals	Missing value imputation for Component Score
	24. Toe flexors	0-4	0-4	8		
Reflexes (NIS-R)	25. Biceps brachii	0-2	0-2	4		Group A
	26. Triceps brachii	0-2	0-2	4		
	27. Brachioradialis	0-2	0-2	4		
	28. Quadriceps femoris	0-2	0-2	4		
	29. triceps surae	0-2	0-2	4	20	
Sensation (NIS-S)	30. Index Finger Touch pressure	0-2	0-2	4		Group A
	31. Index Finger Pin-prick	0-2	0-2	4		
	32. Index Finger Vibration	0-2	0-2	4		
	33. Index Finger Joint position	0-2	0-2	4		
	34. Great Toe Touch pressure	0-2	0-2	4		
	35. Great Toe Pin-prick	0-2	0-2	4		
	36. Great Toe Vibration	0-2	0-2	4		
	37. Great Toe Joint position	0-2	0-2	4	32	
NIS Score (total)					**244**	

Table 2: Modified +7 Score

Component	Assessment	Max Score	Sub-Totals	Missing value imputation for Component Score
Heart rate deep breathing (HRDB)	Heart rate decrease with deep breathing determined with CASE IV	3.72	3.72	Group C
Nerve Conduction Tests	Fibular CMAP amplitude (PMAK)	3.72		Group A
	Tibial CMAP amplitude (TMAK)	3.72		
	Ulnar CMAP amplitude (UMAE)	3.72		
	Ulnar SNAPamplitude (USAW)	3.72		
	Sural SNAPamplitude (SSAB)	3.72	18.6	
Touch-Pressure	Dorsal toes	4		Group A
	Mid-lateral leg	4		
	Mid-anterior thigh	4		
	Anterior lower abdomen	4		
	Mid-upper abdomen	4		
	Anterior subclavicular	4		
	Dorsal finger	4		
	Mid-volar forearm	4		
	Lateral deltoid	4		
	Maxilla of face	4	40	
Heat-Pain	Dorsal toes	4		Group A
	Mid-lateral leg	4		
	Mid-anterior thigh	4	40	

Component	Assessment	**Max Score**	**Sub-** Totals	**Missing value** imputation for Component Score
	Anterior lower abdomen	4		
	Mid-upper abdomen	4		
	Anterior subclavicular	4		
	Dorsal finger	4		
	Mid-volar forearm	4		
	Lateral deltoid	4		
	Maxilla of face	4		
Modified +7 **Score** (Total)			**102.32**	

Table 3: +7 Score

Component	Assessment	**Max Score**	Max Sub-**Totals**	**Missing value imputation for** Component **Score**
Heart rate deep breathing (HRDB)	Heart rate decrease with deep breathing determined with CASE IV	3.72	3.72	Group C
Nerve Conduction Tests	Fibular CMAP amplitude (PMAK)	3.72		Group B
	Fibular MNCV (PMCVK)	3.72		
	Fibular MNDL(PMLA)	3.72		
	Tibial MNDL(TMLA)	3.72		
	Sural SNAPamplitude (SSAB)	3.72	18.6	
Vibration Detection Threshold	Vibration detection threshold of the great toe determined using CASE IV	3.72	3.72	Group C
+7 Score (Total)			**26.04**	

Table 4: NIS-LL Score

Component	Assessment	Right Side	Left Side	Max Score	Max Sub-Totals	Missing value imputation for Component Score
Muscle Weakness for NIS-LL Calculation	17. Hip flexion	0-4	0-4	8	64	
	18. Hip extension	0-4	0-4	8		
	19. Knee flexion	0-4	0-4	8		
	20. Knee extension	0-4	0-4	8		
	21. Ankle dorsiflexors	0-4	0-4	8		
	22. Ankle plantar flexors	0-4	0-4	8		
	23. Toe extensors	0-4	0-4	8		
	24. Toe flexors	0-4	0-4	8		
Reflexes for NIS-LL Calculation	28. Quadriceps femoris	0-2	0-2	4		**Group** A
	29. triceps surae	0-2	0-2	4	8	
Sensation (NIS-S)	34. Great Toe Touch pressure	0-2	0-2	4		**Group** A
	35. Great Toe Pin-prick	0-2	0-2	4		
	36. Great Toe Vibration	0-2	0-2	4		
	37. Great Toe Joint position	0-2	0-2	4	16	
NIS-LL Score (total)					**88**	

Table 5: Sensation Score

Component	Assessment	Right Side	Left Side	Max Score	Max Sub-Totals	Missing value imputation for Component Score
Sensation - Index Finger	30. Index Finger Touch pressure	0-2	0-2	4	20	
	31. Index Finger Pin-prick	0-2	0-2	4		
	32. Index Finger Vibration	0-2	0-2	4		
	33. Index Finger Joint position	0-2	0-2	4		
	29. triceps surae	0-2	0-2	4		
Sensation - Great Toe	34. Great Toe Touch pressure	0-2	0-2	4		
	35. Great Toe Pin-prick	0-2	0-2	4		
	36. Great Toe Vibration	0-2	0-2	4		
	37. Great Toe Joint position	0-2	0-2	4	16	

8.2 Appendix 2 Scoring of Assessment Instruments

Neuropathy Symptoms and Change (NSC)

The NSC questionnaire consists of 38 questions asking about different symptoms.

A symptom is marked as present if in the judgment of the examining neurologist, it occurs more frequently or more severely than in healthy persons of the same age and gender and is due to

neuropathy. If a symptom is present its severity is graded as 1 (slight +), 2 (moderate ++) or 3 (severe +++). If the symptom is not present it is given a score of 0.

Two questions (35 and 36) are only answered by men. These are not included in the score for women.

The questions in the NSC can be divided into the following domains

- Muscle weakness: Questions 1 - 19
- Sensory (hypo / loss of sensation): Questions 20 - 22
- Sensory (paresthesia, hyper sensation): Questions 23 - 29
- Autonomic (GI/Urinary incontinence): Questions 31, 32, 33, 34
- Autonomic (other than GI/Urinary incontinence): Questions 30, 35 - 38 for men
  Questions 30, 37 - 38 for women

The Muscle weakness domain is also divided into 4 sub-domains:

- Head and Neck: Questions 1 - 6
- Chest: Questions 7 - 9
- Upper Limbs: Questions 10 - 15
- Lower Limbs: Questions 16 - 19

For each sub-domain and domain the total score is obtained by summing the relevant questions. The maximum score is therefore 57 for muscle weakness, 9 for Sensory (hypo / loss of sensation), 21 for Sensory (paresthesia, hyper sensation), 12 for Autonomic (GI/Urinary incontinence), 15 for Autonomic (other than GI/Urinary incontinence) in men and 9 for Autonomic (other than GI/Urinary incontinence) in women. The minimum score is zero for each domain.

The NSC total score is the sum of the scores across all 5 domains. The minimum NSC total score is therefore 0 and the maximum NSC total score is 114 for men and 108 for women.

For questions 20-29 the location affected is also collected on the questionnaire but this information is not used in the calculation of the domain or total scores.

The NSC questionnaire also records a change score for the change in symptoms compared to the week before study onset. These are scored as follows

-3 =worse ---

-2 = worse --

-1 = worse -

0 = no change

+1 = better +

+2 = better ++

+3 = better +++

8.3 Appendix 3 Analysis Visit Windows and Follow-Up Visit Window

8.3.1 Table 1. Efficacy Endpoints and PD Endpoints (On-Treatment Analysis Visit Wondow):

Visit window for mNIS+7 and individual components:

	Nominal Visit (Target Day)	**Analysis Visit Window (Day)**
the Parent study	Week 35 (Day 239)	209-269
	Week 66 (Day 456)	411-501
The OLE study	Week 26 (Day 176)	146 - 206
	Week 52 (Day 358)	328 - 388
	Week 78 (Day 540)	510 - 570
	Week 104 (Day 722)	692 - 752
	Week 130 (Day 904)	874 - 934
	Week 156 (Day 1086)	1041-1131

Visit window for NIS and individual components, NSC, Norfolk QOL-DN and individual components:

	Nominal Visit (Target Day)	**Analysis Visit Window (Day)**
the Parent study	Week 35 (Day 239)	209-269
	Week 66 (Day 456)	411-501
The OLE study	Week 26 (Day 176)	146 - 206
	Week 52 (Day 358)	328 - 388
	Week 78 (Day 540)	510 - 570
	Week 104 (Day 722)	692 - 752
	Week 130 (Day 904)	874 - 934
	Week 156 (Day 1086)	1041-1131
	Y4-W52 (Day 1450)	1420 - 1480
	Y5-W52 (Day 1814)	1784 - 1844

Visit window for SF-36 Questionnaire and PND Score:

	Nominal Visit (Target Day)	**Analysis Visit Window (Day)**
the Parent study	Week 35 (Day 240)	210-270
	Week 65 (Day 449)	397-501
The OLE study	Week 26 (Day 176)	146 - 206
	Week 52 (Day 358)	328 - 388
	Week 78 (Day 540)	510 - 570

	Nominal Visit (Target Day)	Analysis Visit Window (Day)
	Week 104 (Day 722)	692 - 752
	Week 130 (Day 904)	874 - 934
	Week 156 (Day 1086)	1041 - 1131
	Y4-W52 (Day 1450)	1420 - 1480
	Y5-W52 (Day 1814)	1784 - 1844

Visit window for Body Weight, BMI and mBMI:

	Nominal Visit (Target Day)	Analysis Visit Window (Day)
the Parent study	Week 13 (Day 85)	55-115
	Week 35 (Day 240)	210-270
	Week 53 (Day 365)	335-395
	Week 65 (Day 449)	419-479
The OLE study	Week 13 (Day 85)	55-115
	Week 26 (Day 176)	146-206
	Week 52 (Day 358)	328-388
	Week 78 (Day 540)	510-570
	Week 104 (Day 722)	692-752
	Week 130 (Day 904)	874-934
	Week 156 (Day 1086)	1056-1116

Visit window for PD Panel (TTR and RBP4):

	Nominal Visit (Target Day)	Analysis Visit Window (Day)
the Parent study	Week 3 (Day 15)	2-21
	Week 5 (Day 29)	22-38
	Week 8 (Day 50)	39-66
	Week 13 (Day 85)	67-101
	Week 18 (Day 120)	102-136
	Week 23 (Day 155)	137-175
	Week 29 (Day 197)	176-217
	Week 35 (Day 240)	218-259
	Week 41 (Day 281)	260-301
	Week 47 (Day 323)	302343
	Week 53 (Day 365)	344-385
	Week 59 (Day 407)	386-427
	Week 65 (Day 449)	428-469

	Nominal Visit (Target Day)	Analysis Visit Window (Day)
The OLE study	Week 7 (Day 43)	13-63
	Week 13 (Day 85)	64-101
	Week 18 (Day 120)	102-129
	Week 21 (Day 141)	130-157
	Week 26 (Day 176)	158-206
	Week 39 (Day 267)	237-297
	Week 52 (Day 358)	328-388
	Week 65(Day 449)	419-479
	Week 78 (Day 540)	510-570
	Week 91 (Day 631)	601-661
	Week 104 (Day 722)	692-752
	Week 117 (Day 813)	783-843
	Week 130 (Day 904)	874-934
	Week 143 (Day 995)	965-1025
	Week 156 (Day 1086)	1056-1116
	Y4-W13 (Day 1177)	1147-1207
	Y4-W26 (Day 1268)	1238-1298
	Y4-W39 (Day 1359)	1329-1389
	Y4-W52 (Day 1450)	1420-1480
	Y5-W13 (Day 1541)	1511-1571
	Y5-W26 (Day 1632)	1602-1662
	Y5-W39 (Day 1723)	1693-1753
	Y5-W52 (Day 1814)	1784-1844

Visit window for NT-proBNP:

	Nominal Visit (Target Day)	Analysis Visit Window (Day)
the Parent study	Week 13 (Day 85)	55-115
	Week 35 (Day 240)	210-270
	Week 65 (Day 449)	397-501
The OLE study	Week 7 (Day 43)	13-63
	Week 13 (Day 85)	64-101
	Week 18 (Day 120)	102-147
	Week 26 (Day 176)	148-206
	Week 39 (Day 267)	237-297
	Week 52 (Day 358)	328-388
	Week 65(Day 449)	419-479

	Nominal Visit (Target Day)	Analysis Visit Window (Day)
	Week 78 (Day 540)	510-570
	Week 91 (Day 631)	601-661
	Week 104 (Day 722)	692-752
	Week 117 (Day 813)	783-843
	Week 130 (Day 904)	874-934
	Week 143 (Day 995)	965-1025
	Week 156 (Day 1086)	1041-1131
	Y4-W13 (Day 1177)	1147-1207
	Y4-W26 (Day 1268)	1238-1298
	Y4-W39 (Day 1359)	1329-1389
	Y4-W52 (Day 1450)	1420-1480
	Y5-W13 (Day 1541)	1511-1571
	Y5-W26 (Day 1632)	1602-1662
	Y5-W39 (Day 1723)	1693-1753
	Y5-W52 (Day 1814)	1784-1844

8.3.2 Table 2. Efficacy Endpoints and PD Endpoints (Post-Treatment Analysis Follow-Up Visit Wondow):

Efficacy/PD measure	Weeks from last dose (Days from last dose)	Analysis Visit Window (Days from last dose)
NT-proBNP;	Follow-up Week 13 (91)	61-121
BMI and mBMI; PD Panel (TTR and RBP4);	Follow-up Week 13 (91)	61-121

8.3.3 Table 3. Safety Endpoints (On-Treatment Analysis Visit Wondow):

Vital Signs and Retinol and Retinyl palmitate

Safety endpoint	**Nominal Visit (Target Day)**	**Analysis Visit Window (Day)**
The OLE study	Week 7 (Day 43)	22-63
	Week 13 (Day 85)	64-115
	Week 26 (Day 176)	146-206
	Week 52 (Day 358)	328-388
	Week 78 (Day 540)	510-570
	Week 104 (Day 722)	629-752
	Week 130 (Day 904)	874-934
	Week 156 (Day 1086)	1056-1116
	Y4-W26 (Day 1268)	1238-1298
	Y4-W52 (Day 1450)	1420-1480
	Y5-W26 (Day 1632)	1602-1662
	Y5-W52 (Day 1814)	1784-1844

Body Weight

Safety endpoint	**Nominal Visit (Target Day)**	**Analysis Visit Window (Day)**
The OLE study	Week 13 (Day 85)	55-115
	Week 26 (Day 176)	146-206
	Week 52 (Day 358)	328-388
	Week 78 (Day 540)	510-570
	Week 104 (Day 722)	629-752
	Week 130 (Day 904)	874-934
	Week 156 (Day 1086)	1056-1116

ECG

Safety endpoint	**Nominal Visit (Target Day)**	**Analysis Visit Window (Day)**
The OLE study	Week 26 (Day 176)	146-206
	Week 52 (Day 358)	328-388
	Week 78 (Day 540)	510-570
	Week 104 (Day 722)	629-752
	Week 130 (Day 904)	874-934
	Week 156 (Day 1086)	1056-1116
	Y4-W26 (Day 1268)	1238-1298
	Y4-W52 (Day 1450)	1420-1480
	Y5-W26 (Day 1632)	1602-1662

Safety endpoint	Nominal Visit (Target Day)	Analysis Visit Window (Day)
	Y5-W52 (Day 1814)	1784-1844

Chemistry Panel, Hematology and Urinalysis

Safety endpoint	Nominal Visit (Target Day)	Analysis Visit Window (Day)
The OLE study	Week 4 (Day 22)	11-31
	Week 7 (Day 43)	32-52
	Week 10 (Day 64)	53-73
	Week 13 (Day 85)	74-91
	Week 15 (Day 99)	92-108
	Week 18 (Day 120)	109-129
	Week 21 (Day 141)	130-147
	Week 23 (Day 155)	148-164
	Week 26 (Day 176)	165-185
	Week 29 (Day 197)	186-227
	Week 39 (Day 267)	237-297
	Week 52 (Day 358)	328-388
	Week 65 (Day 449)	419-479
	Week 78 (Day 540)	510-570
	Week 91 (Day 631)	601-661
	Week 104 (Day 722)	692-752
	Week 117 (Day 813)	783-843
	Week 130 (Day 904)	874-934
	Week 143 (Day 995)	965-1025
	Week 156 (Day 1086)	1056-1116
	Y4-W13 (Day 1177)	1147-1207
	Y4-W26 (Day 1268)	1238-1298
	Y4-W39 (Day 1359)	1329-1389
	Y4-W52 (Day 1450)	1420-1480
	Y5-W13 (Day 1541)	1511-1571
	Y5-W26 (Day 1632)	1602-1662
	Y5-W39 (Day 1723)	1693-1753
	Y5-W52 (Day 1814)	1784-1844

Serum Creatinine

Safety endpoint	Nominal Visit (Target Day)	Analysis Visit Window (Day)
The OLE study	Week 4 (Day 22)	11-31
	Week 7 (Day 43)	32-52

Safety endpoint	Nominal Visit (Target Day)	Analysis Visit Window (Day)
	Week 10 (Day 64)	53-73
	Week 13 (Day 85)	74-91
	Week 15 (Day 99)	92-108
	Week 18 (Day 120)	109-129
	Week 21 (Day 141)	130-147
	Week 23 (Day 155)	148-164
	Week 26 (Day 176)	165-185
	Week 29 (Day 197)	186-203
	Week 31 (Day 211)	204-217
	Week 33 (Day 225)	218-231
	Week 35 (Day 239)	232-245
	Week 37 (Day 253)	246-259
	Week 39 (Day 267)	260-273
	Week 41 (Day 281)	274-287
	Week 43 (Day 295)	288-301
	Week 45 (Day 309)	302-315
	Week 47 (Day 323)	316-329
	Week 49 (Day 337)	330-346
	Week 52 (Day 358)	347-364
	Week 54 (Day 372)	365-378
	Week 56 (Day 386)	379-392
	Week 58 (Day 400)	393-406
	Week 60 (Day 414)	407-420
	Week 62 (Day 428)	421-437
	Week 65 (Day 449)	438-455
	Week 67 (Day 463)	456-469
	Week 69 (Day 477)	470-483
	Week 71 (Day 491)	484-497
	Week 73 (Day 505)	498-511
	Week 75 (Day 519)	512-528
	Week 78 (Day 540)	529-546
	Week 80 (Day 554)	547-560
	Week 82 (Day 568)	561-574
	Week 84 (Day 582)	575-588
	Week 86 (Day 596)	589-602
	Week 88 (Day 610)	603-619
	Week 91 (Day 631)	620-637
	Week 93 (Day 645)	638-651

Safety endpoint	Nominal Visit (Target Day)	Analysis Visit Window (Day)
	Week 95 (Day 659)	652-665
	Week 97 (Day 673)	666-679
	Week 99 (Day 687)	680-693
	Week 101 (Day 701)	694-710
	Week 104 (Day 722)	711-728
	Week 106 (Day 736)	729-742
	Week 108 (Day 750)	743-756
	Week 110 (Day 764)	757-770
	Week 112 (Day 778)	771-784
	Week 114 (Day 792)	785-801
	Week 117 (Day 813)	802-819
	Week 119 (Day 827)	820-833
	Week 121 (Day 841)	834-847
	Week 123 (Day 855)	848-861
	Week 125 (Day 869)	862-875
	Week 127 (Day 883)	876-892
	Week 130 (Day 904)	893-910
	Week 132 (Day 918)	911-924
	Week 134 (Day 932)	925-938
	Week 136 (Day 946)	939-952
	Week 138 (Day 960)	953-966
	Week 140 (Day 974)	967-983
	Week 143 (Day 995)	984-1001
	Week 145 (Day 1009)	1002-1015
	Week 147 (Day 1023)	1016-1029
	Week 149 (Day 1037)	1030-1043
	Week 151 (Day 1051)	1044-1057
	Week 153 (Day 1065)	1058-1074
	Week 156 (Day 1086)	1075-1092
	Y4-W2 (Day 1100)	1093-1106
	Y4-W4 (Day 1114)	1107-1120
	Y4-W6 (Day 1128)	1121-1134
	Y4-W8 (Day 1142)	1135-1148
	Y4-W10 (Day 1156)	1149-1165
	Y4-W13 (Day 1177)	1166-1183
	Y4-W15 (Day 1191)	1184-1197
	Y4-W17 (Day 1205)	1198-1211
	Y4-W19 (Day 1219)	1212-1225

Safety endpoint	Nominal Visit (Target Day)	Analysis Visit Window (Day)
	Y4-W21 (Day 1233)	1226-1239
	Y4-W23 (Day 1247)	1240-1256
	Y4-W26 (Day 1268)	1257-1274
	Y4-W28 (Day 1282)	1275-1288
	Y4-W30 (Day 1296)	1289-1302
	Y4-W32 (Day 1310)	1303-1316
	Y4-W34 (Day 1324)	1317-1330
	Y4-W36 (Day 1338)	1331-1347
	Y4-W39 (Day 1359)	1348-1365
	Y4-W41 (Day 1373)	1366-1379
	Y4-W43 (Day 1387)	1380-1393
	Y4-W45 (Day 1401)	1394-1407
	Y4-W47 (Day 1415)	1408-1421
	Y4-W49 (Day 1429)	1422-1438
	Y4-W52 (Day 1450)	1439-1456
	Y5-W2 (Day 1464)	1457-1470
	Y5-W4 (Day 1478)	1471-1484
	Y5-W6 (Day 1492)	1485-1498
	Y5-W8 (Day 1506)	1499-1512
	Y5-W10 (Day 1520)	1513-1529
	Y5-W13 (Day 1541)	1530-1547
	Y5-W15 (Day 1555)	1548-1561
	Y5-W17 (Day 1569)	1562-1575
	Y5-W19 (Day 1583)	1576-1589
	Y5-W21 (Day 1597)	1590-1603
	Y5-W23 (Day 1611)	1604-1620
	Y5-W26 (Day 1632)	1621-1638
	Y5-W28 (Day 1646)	1639-1652
	Y5-W30 (Day 1660)	1653-1666
	Y5-W32 (Day 1674)	1667-1680
	Y5-W34 (Day 1688)	1681-1694
	Y5-W36 (Day 1702)	1695-1711
	Y5-W39 (Day 1723)	1712-1729
	Y5-W41 (Day 1737)	1730-1743
	Y5-W43 (Day 1751)	1744-1757
	Y5-W45 (Day 1765)	1758-1771
	Y5-W47 (Day 1779)	1772-1785
	Y5-W49 (Day 1793)	1786-1802

Safety endpoint	Nominal Visit (Target Day)	Analysis Visit Window (Day)
	Y5-W52 (Day 1814)	1803-1820

Platelets (weekly)

Safety endpoint	Nominal Visit (Target Day)	Analysis Visit Window (Day)
The OLE study	Week 2 (Day 8)	7-11
	Week 3 (Day 15)	12-17
	Week 4 (Day 22)	18-24
	Week 5 (Day 29)	25-31
	Week 6 (Day 36)	32-38
	Week 7 (Day 43)	39-45
	Week 8 (Day 50)	46-52
	Week 9 (Day 57)	53-59
	Week 10 (Day 64)	60-66
	Week 11 (Day 71)	67-73
	Week 12 (Day 78)	74-80
	Week 13 (Day 85)	81-87
	Week 14 (Day 92)	88-94
	Week 15 (Day 99)	95-101
	Week 16 (Day 106)	102-108
	Week 17 (Day 113)	109-115
	Week 18 (Day 120)	116-122
	Week 19 (Day 127)	123-129
	Week 20 (Day 134)	130-136
	Week 21 (Day 141)	137-143
	Week 22 (Day 148)	144-150
	Week 23 (Day 155)	151-157
	Week 24 (Day 162)	158-164
	Week 25 (Day 169)	165-171
	Week 26 (Day 176)	172-178
	Week 27 (Day 183)	179-185
	Week 28 (Day 190)	186-192
	Week 29 (Day 197)	193-199
	Week 30 (Day 204)	200-206
	Week 31 (Day 211)	207-213
	Week 32 (Day 218)	214-220
	Week 33 (Day 225)	221-227
	Week 34 (Day 232)	228-235

Safety endpoint	Nominal Visit (Target Day)	Analysis Visit Window (Day)
	Week 35 (Day 240)	236-242
	Week 36 (Day 246)	243-248
	Week 37 (Day 253)	249-255
	Week 38 (Day 260)	256-262
	Week 39 (Day 267)	263-269
	Week 40 (Day 274)	270-276
	Week 41 (Day 281)	277-283
	Week 42 (Day 288)	284-290
	Week 43 (Day 295)	291-297
	Week 44 (Day 302)	298-304
	Week 45 (Day 309)	305-311
	Week 46 (Day 316)	312-318
	Week 47 (Day 323)	319-325
	Week 48 (Day 330)	326-332
	Week 49 (Day 337)	333-339
	Week 50 (Day 344)	340-346
	Week 51 (Day 351)	347-353
	Week 52 (Day 358)	354-360
	Week 53 (Day 365)	361-367
	Week 54 (Day 372)	368-374
	Week 55 (Day 379)	375-381
	Week 56 (Day 386)	382-388
	Week 57 (Day 393)	389-395
	Week 58 (Day 400)	396-402
	Week 59 (Day 407)	403-409
	Week 60 (Day 414)	410-416
	Week 61 (Day 421)	417-423
	Week 62 (Day 428)	424-430
	Week 63 (Day 435)	431-437
	Week 64 (Day 442)	438-444
	Week 65 (Day 449)	445-451
	Week 66 (Day 456)	452-458
	Week 67 (Day 463)	459-465
	Week 68 (Day 470)	466-472
	Week 69 (Day 477)	473-479
	Week 70 (Day 484)	480-486
	Week 71 (Day 491)	487-493
	Week 72 (Day 498)	494-500

Safety endpoint	Nominal Visit (Target Day)	Analysis Visit Window (Day)
	Week 73 (Day 505)	501-507
	Week 74 (Day 512)	508-514
	Week 75 (Day 519)	515-521
	Week 76 (Day 526)	522-528
	Week 77 (Day 533)	529-535
	Week 78 (Day 540)	536-542
	Week 79 (Day 547)	543-549
	Week 80 (Day 554)	550-556
	Week 81 (Day 561)	557-563
	Week 82 (Day 568)	564-570
	Week 83 (Day 575)	571-577
	Week 84 (Day 582)	578-584
	Week 85 (Day 589)	585-591
	Week 86 (Day 596)	592-598
	Week 87 (Day 603)	599-605
	Week 88 (Day 610)	606-612
	Week 89(Day 617)	613-619
	Week 90 (Day 624)	620-626
	Week 91 (Day 631)	627-633
	Week 92 (Day 638)	634-640
	Week 93 (Day 645)	641-647
	Week 94 (Day 652)	648-654
	Week 95 (Day 659)	655-661
	Week 96 (Day 666)	662-668
	Week 97 (Day 673)	669-675
	Week 98 (Day 680)	676-682
	Week 99 (Day 687)	683-689
	Week 100 (Day 694)	690-696
	Week 101 (Day 701)	697-703
	Week 102 (Day 708)	704-710
	Week 103 (Day 715)	711-717
	Week 104 (Day 722)	718-724
	Week 105 (Day 729)	725-731
	Week 106 (Day 736)	732-738
	Week 107 (Day 743)	739-745
	Week 108 (Day 750)	746-752
	Week 109 (Day 757)	753-759
	Week 110 (Day 764)	760-766

Safety endpoint	Nominal Visit (Target Day)	Analysis Visit Window (Day)
	Week 111 (Day 771)	767-773
	Week 112 (Day 778)	774-780
	Week 113 (Day 785)	781-787
	Week 114 (Day 792)	788-794
	Week 115 (Day 799)	795-801
	Week 116 (Day 806)	802-808
	Week 117 (Day 813)	809-815
	Week 118 (Day 820)	816-822
	Week 119 (Day 827)	823-829
	Week 120 (Day 834)	830-836
	Week 121 (Day 841)	837-843
	Week 122 (Day 848)	844-850
	Week 123 (Day 855)	851-857
	Week 124 (Day 862)	858-864
	Week 125 (Day 869)	865-871
	Week 126 (Day 876)	872-878
	Week 127 (Day 883)	879-885
	Week 128 (Day 890)	886-892
	Week 129 (Day 897)	893-899
	Week 130 (Day 904)	900-906
	Week 131 (Day 911)	907-913
	Week 132 (Day 918)	914-920
	Week 133 (Day 925)	921-927
	Week 134 (Day 932)	928-934
	Week 135 (Day 939)	935-941
	Week 136 (Day 946)	942-948
	Week 137 (Day 953)	949-955
	Week 138 (Day 960)	956-962
	Week 139 (Day 967)	963-969
	Week 140 (Day 974)	970-976
	Week 141 (Day 981)	977-983
	Week 142 (Day 988)	984-990
	Week 143 (Day 995)	991-997
	Week 144 (Day 1002)	998-1004
	Week 145 (Day 1009)	1005-1011
	Week 146 (Day 1016)	1012-1018
	Week 147 (Day 1023)	1019-1025
	Week 148 (Day 1030)	1026-1032

Safety endpoint	Nominal Visit (Target Day)	Analysis Visit Window (Day)
	Week 149 (Day 1037)	1033-1039
	Week 150 (Day 1044)	1040-1046
	Week 151 (Day 1051)	1047-1053
	Week 152 (Day 1058)	1054-1060
	Week 153 (Day 1065)	1061-1067
	Week 154 (Day 1072)	1068-1074
	Week 155 (Day 1079)	1075-1081
	Week 156 (Day 1086)	1082-1088
	Y4-W1 (Day 1093)	1089-1095
	Y4-W2 (Day 1100)	1096-1102
	Y4-W3 (Day 1107)	1103-1109
	Y4-W4 (Day 1114)	1110-1116
	Y4-W5 (Day 1121)	1117-1123
	Y4-W6 (Day 1128)	1124-1130
	Y4-W7 (Day 1135)	1131-1137
	Y4-W8 (Day 1142)	1138-1144
	Y4-W9 (Day 1149)	1145-1151
	Y4-W10 (Day 1156)	1152-1158
	Y4-W11 (Day 1163)	1159-1165
	Y4-W12 (Day 1170)	1166-1172
	Y4-W13 (Day 1177)	1173-1179
	Y4-W14 (Day 1184)	1180-1186
	Y4-W15 (Day 1191)	1187-1193
	Y4-W16 (Day 1198)	1194-1200
	Y4-W17 (Day 1205)	1201-1207
	Y4-W18 (Day 1212)	1208-1214
	Y4-W19 (Day 1219)	1215-1221
	Y4-W20 (Day 1226)	1222-1228
	Y4-W21 (Day 1233)	1229-1235
	Y4-W22 (Day 1240)	1236-1242
	Y4-W23 (Day 1247)	1243-1249
	Y4-W24 (Day 1254)	1250-1256
	Y4-W25 (Day 1261)	1257-1263
	Y4-W26 (Day 1268)	1264-1270
	Y4-W27 (Day 1275)	1271-1277
	Y4-W28 (Day 1282)	1278-1284
	Y4-W29 (Day 1289)	1285-1291
	Y4-W30 (Day 1296)	1292-1298

Safety endpoint	Nominal Visit (Target Day)	Analysis Visit Window (Day)
	Y4-W31 (Day 1303)	1299-1305
	Y4-W32 (Day 1310)	1306-1312
	Y4-W33 (Day 1317)	1313-1319
	Y4-W34 (Day 1324)	1320-1326
	Y4-W35 (Day 1331)	1327-1333
	Y4-W36 (Day 1338)	1334-1340
	Y4-W37 (Day 1345)	1341-1347
	Y4-W38 (Day 1352)	1348-1354
	Y4-W39 (Day 1359)	1355-1361
	Y4-W40 (Day 1366)	1362-1368
	Y4-W41 (Day 1373)	1369-1375
	Y4-W42 (Day 1380)	1376-1382
	Y4-W43 (Day 1387)	1383-1389
	Y4-W44 (Day 1394)	1390-1396
	Y4-W45 (Day 1401)	1397-1403
	Y4-W46 (Day 1408)	1404-1410
	Y4-W47 (Day 1415)	1411-1417
	Y4-W48 (Day 1422)	1418-1424
	Y4-W49 (Day 1429)	1425-1431
	Y4-W50 (Day 1436)	1432-1438
	Y4-W51 (Day 1443)	1439-1445
	Y4-W52 (Day 1450)	1446-1452
	Y5-W1 (Day 1457)	1453-1459
	Y5-W2 (Day 1464)	1460-1466
	Y5-W3 (Day 1471)	1467-1473
	Y5-W4 (Day 1478)	1474-1480
	Y5-W5 (Day 1485)	1481-1487
	Y5-W6 (Day 1492)	1488-1494
	Y5-W7 (Day 1499)	1495-1501
	Y5-W8 (Day 1506)	1502-1508
	Y5-W9 (Day 1513)	1509-1515
	Y5-W10 (Day 1520)	1516-1522
	Y5-W11 (Day 1527)	1523-1529
	Y5-W12 (Day 1534)	1530-1536
	Y5-W13 (Day 1541)	1537-1543
	Y5-W14 (Day 1548)	1544-1550
	Y5-W15 (Day 1555)	1551-1557
	Y5-W16 (Day 1562)	1558-1564

Safety endpoint	Nominal Visit (Target Day)	Analysis Visit Window (Day)
	Y5-W17 (Day 1569)	1565-1571
	Y5-W18 (Day 1576)	1572-1578
	Y5-W19 (Day 1583)	1579-1585
	Y5-W20 (Day 1590)	1586-1592
	Y5-W21 (Day 1597)	1593-1599
	Y5-W22 (Day 1604)	1600-1606
	Y5-W23 (Day 1611)	1607-1613
	Y5-W24 (Day 1618)	1614-1620
	Y5-W25 (Day 1625)	1621-1627
	Y5-W26 (Day 1632)	1628-1634
	Y5-W27 (Day 1639)	1635-1641
	Y5-W28 (Day 1646)	1642-1648
	Y5-W29 (Day 1653)	1649-1655
	Y5-W30 (Day 1660)	1656-1662
	Y5-W31 (Day 1667)	1663-1669
	Y5-W32 (Day 1674)	1670-1676
	Y5-W33 (Day 1681)	1677-1683
	Y5-W34 (Day 1688)	1684-1690
	Y5-W35 (Day 1695)	1691-1697
	Y5-W36 (Day 1702)	1698-1704
	Y5-W37 (Day 1709)	1705-1711
	Y5-W38 (Day 1716)	1712-1718
	Y5-W39 (Day 1723)	1719-1725
	Y5-W40 (Day 1730)	1726-1732
	Y5-W41 (Day 1737)	1733-1739
	Y5-W42 (Day 1744)	1740-1746
	Y5-W43 (Day 1751)	1747-1753
	Y5-W44 (Day 1758)	1754-1760
	Y5-W45 (Day 1765)	1761-1767
	Y5-W46 (Day 1772)	1768-1774
	Y5-W47 (Day 1779)	1775-1781
	Y5-W48 (Day 1786)	1782-1788
	Y5-W49 (Day 1793)	1789-1795
	Y5-W50 (Day 1800)	1796-1802
	Y5-W51 (Day 1807)	1803-1809
	Y5-W52 (Day 1814)	1810-1816

Thyroid Panel and Coagulation: PT, aPTT, INR

Safety endpoint	Nominal Visit (Target Day)	Analysis Visit Window (Day)
The OLE study	Week 7 (Day 43)	13-63
	Week 13 (Day 85)	64-115
	Week 26 (Day 176)	146-206
	Week 52 (Day 358)	328-388
	Week 78 (Day 540)	510-570
	Week 104 (Day 722)	629-752
	Week 156 (Day 1086)	1056-1116
	Y4-W26 (Day 1268)	1238-1298
	Y4-W52 (Day 1450)	1420-1480
	Y5-W52 (Day 1814)	1784-1844

[†]ISIS 420915 baseline for patients took placebo in the parent study.

Immunogenicity

Safety endpoint	Nominal Visit (Target Day)	Analysis Visit Window (Day)
The OLE study	Week 7 (Day 43)	13-63
	Week 13 (Day 85)	64-101
	Week 18 (Day 120)	102-147
	Week 26 (Day 176)	148-206
	Week 39 (Day 267)	237-297
	Week 52 (Day 358)	328-388
	Week 65(Day 449)	419-479
	Week 78 (Day 540)	510-570
	Week 91 (Day 631)	601-661
	Week 104 (Day 722)	692-752
	Week 117 (Day 813)	783-843
	Week 130 (Day 904)	874-934
	Week 143 (Day 995)	965-1025
	Week 156 (Day 1086)	1056-1116
	Y4-W52 (Day 1450)	1420-1480
	Y5-W52 (Day 1814)	1784-1844

ERG

Safety endpoint	Nominal Visit (Target Day)	Analysis Visit Window (Day)
The OLE study	Week 78 (Day 540)	510-570
	Week 156 (Day 1086)	1056-1116

Ophthalmology

Safety endpoint	Nominal Visit (Target Day)	Analysis Visit Window (Day)
The OLE study	Week 26 (Day 176)	146-206
	Week 52 (Day 358)	328-388
	Week 78 (Day 540)	510-570
	Week 104 (Day 772)	742-802
	Week 130 (Day 904)	874-934
	Week 156 (Day 1086)	1056-1116
	Y4-W26 (Day 1268)	1238-1298
	Y4-W52 (Day 1450)	1420-1480
	Y5-W26 (Day 1632)	1602-1662
	Y5-W52 (Day 1814)	1784-1844

Inflammatory Panel: Hs-CRP

Safety endpoint	Nominal Visit (Target Day)	Analysis Visit Window (Day)
The OLE study	Week 7 (Day 43)	22-63
	Week 13 (Day 85)	64-115
	Week 26 (Day 176)	146-206
	Week 52 (Day 358)	328-388
	Week 78 (Day 540)	510-570
	Week 91 (Day 631)	601-661
	Week 104 (Day 722)	692-752
	Week 117 (Day 813)	783-843
	Week 130 (Day 904)	874-934
	Week 143 (Day 995)	965-1025
	Week 156 (Day 1086)	1056-1116
	Y4-W26 (Day 1268)	1238-1298
	Y4-W39 (Day 1359)	1329-1389
	Y4-W52 (Day 1450)	1420-1480
	Y5-W13 (Day 1541)	1511-1571
	Y5-W26 (Day 1632)	1602-1662
	Y5-W39 (Day 1723)	1693-1753
	Y5-W52 (Day 1814)	1784-1844

8.3.4 Table 4. Safety Endpoints (Post-Treatment Analysis Follow-Up Visit Wondow):

Safety endpoint	Weeks from last dose (Days from last dose)	Analysis Visit Window (Days from last dose)
Vital Signs; Body Weight, ECG; Chemistry Panel; Hematology; Urinalysis; Thyroid Panel; Coagulation: PT, aPTT, INR; Retinol and Retinyl palmitate; Inflammatory Panel: Hs-CRP; Immunogenicity	Follow-up Week 13 (91)	61-121
Serum Creatinine	Follow-up Week 2 (14)	8-20
	Follow-up Week 4 (28)	21-34
	Follow-up Week 6 (42)	35-65
	Follow-up Week 13 (91)	66-121
Platelets		
	Follow-up Week 2 (14)	10-16
	Follow-up Week 3 (21)	17-23
	Follow-up Week 4 (28)	24-30
	Follow-up Week 5 (35)	31-37
	Follow-up Week 6 (42)	38-65
	Follow-up Week 13 (91)	66-121

9. Updates and Additional Analysis in Final Analyses

CS3 final analysis will perform when OLE study completed.

9.1 Analyses Removed from Final Analyses

Per protocol set (PPS) flag will not created in final ADaM dataset and Efficacy and PD analysis based on PPS will not be performed.

Efficacy analysese by subgroup will not be performed.

The degree of progression for mNIS+7 and Norfolk (specified in section 3.4.2.1) will not be performed

The proportion of patients with percentage decrease from either the parent study baseline or the OLE study baseline in plasma transthyretin (TTR) $\geq$ 60% (specified in section 3.5) will not be performed.

9.2 Additional Analyses added for Final Analyses

9.2.1 Based on OLE data only

- Summary of disposition and protocol deviation associated with COVID-19 based on CS3 Enrolled Patients
- Summary of ISIS 420915 Trough Plasma Concentrations (On-Study) based on safety set.
- Summary of Complement Results (Complement C3, Complement C4, Complement Split Bb, Complement Split C5a) by visit based on safety set
- Summary of TEAE by System Organ Class and Preferred Term and by PND score (On-Study) based on safety set
- Lab shift table for Hematology (Hemoglobin, Lymphocyte, Neutrophil, White Blood Cell), Chemistry Test, Coagulation Test, Urinalysis test, Urinalysis Results from Central Lab Based on 24-hr Urine Collections, Confirmed Peak ALT, Confirmed Peak AST, Confirmed Peak Total Bilirubin (On-study) based on safety set.
- Incidence of Post-baseline abnormality, including lab Complement Results, vital signs and body weight and QTcF.

- Efficacacy endpoints

  <u>On-treatment:</u> Add Statistical Analysis of Change from CS2 Baseline to efficacy endpoints:

  mNIS+7, NIS+7, NIS, Modified +7, +7, NSC composite and component score, mNIS+7 composite score, Norfolk QOL-DN, NSC total and domain score and selected questions, SF-36 component and Domain Scores. Norfolk QOL-DN Symptoms Domain Score based on Stage 1 Patients, Norfolk QOL-DN Physical Functioning/Large Fiber Neuropathy Domain Score based on Stage 2 Patients

  <u>Post-treatment:</u>
  Show Descriptive statistics of absolute value, change from baseline and percent change from baseline in mNIS+7, NIS+7, NIS, Modified +7, +7 Composite and Component, Norfolk QOL-DN Total and Domain Scores, SF-36 Scores, NSC score and Select Questions from NSC

9.2.2 Based on both CS2 and CS3 data

CS3 final CRS will include some outputs from 420915 ISS, Please reference 420915 ISS SAP for planned statistical analyses and definition in details. Below are updates were added based on CS3 final CRS additional request

9.2.2.1 Add More Population Definition

- ISIS 420915 Full Analysis Set (ISIS 420915 FAS) will be subset of CS2 or CS3 FAS patients who received at least 1 injection of ISIS 420915 in CS2 or CS3 studies.
- ISIS 420915 ECHO subgroup will be the subset of CS2 ECHO subgroup patients who received at least 1 injection of ISIS 420915 in CS2 or CS3 studies.
- ISIS 420915 CM-ECHO Set will be the subset of CS2 CM-ECHO Set patients who received at least 1 injection of ISIS 420915 in CS2 or CS3 studies.
- ISIS 420915 PK Set will include all patients who received at least one dose of ISIS 420915 and have at least one evaluable PK sample collected and analyzed with reportable result in CS2 or CS3 studies.

9.2.2.2 Study Period Definition (On-Treatment, Post-Treatment and On-Study)

<u>On-Treatment</u>

- For efficacy endpoints except BMI, mBMI and PD, on-treatment period starts from ISIS 420915 **Study Day 1** until 52 days after the last dose of ISIS 420915.
- For BMI, mBMI, PD and Safety endpoint ERG, on-treatment period is from ISIS 420915 **Study Day 1** until 28 days after the last dose of ISIS 420915
- For other Safety endpoints except ERG, on-treatment period is from ISIS 420915 **Study Day 1** until 7 days after the last dose of ISIS 420915

<u>Post-Treatment</u>

- Post-treatment period starts on the day after the on-treatment period and ends on the day of the patient's last contact date within the study.

<u>On-Study</u>

- On-Study starts from ISIS 420915 **Study Day 1** until the patient's last contact date.

Of note, the definition above only apply for CS2 and CS3 combined data summary, which is not conflict with section 3.2.1.1.4

9.2.2.3 Itegrated Summary of Efficacy based on CS2 and CS3 data

Descriptive summary statistics:

Descriptive summary statistics for absolute values, change or percent change from ISIS 420915 baseline, if applicable, will be provided by analysis visits for below endpoints based on 420915 FAS, unless specify.

- mNIS+7 Composite Score (On-Treatment)
- mNIS+7 Composite Score (On-Treatment) by IM
- Modified +7 and +7 Composite Scores (On-Treatment)
- NIS+7 Composite Scores (On-Treatment)
- NIS Composite and Component Scores (On-Treatment)
- Modified +7 Component Scores (On-Treatment)
- +7 Component Scores (On-Treatment)
- Norfolk QOL-DN Total Score (On-Treatment)
- Norfolk QOL-DN Total Score (On-Treatment) by IM
- Norfolk QOL-DN Symptoms Domain Score (On-Treatment) - Stage 1 Patients
- Norfolk QOL-DN Physical Functioning/Large Fiber Neuropathy Domain Score (On-Treatment) - Stage 2 Patients
- Norfolk QOL-DN Domain Scores (On-Treatment)
- NSC Total Score and Domain Scores (On-Treatment)
- Modified Body Mass Index and Body Mass Index (On-Treatment)
- Transthyretin (TTR) and Retinol Binding Protein 4 (RBP4) (On-Treatment)
- Transthyretin (TTR) (On-Treatment) by IM
- SF-36 Component Summary Scores and Domain Scores (On-Treatment)
- NT-proBNP Result (pmol/L) and Log-Transformed NT-proBNP Result (On-Treatment), outputs will be repeated based on ISIS 420915 CM-ECHO set
- mNIS+7, NIS+7, NIS, Modified +7, +7 Composite and Component Scores (Post-Treatment)
- Norfolk QOL-DN Total and Domain Scores (Post-Treatment)
- SF-36 Scores (Post-Treatment)
- NSC Score (Post-Treatment)
- Global Longitudinal Strain (%) (On-Treatment) based on ISIS 420915 Enrolled Patients, ISIS 420915 ECHO Subgroup, and ISIS 420915 CM-ECHO Set
- Assessment of Global Left Ventricular Size and Function - LV Mass (g) (On-Treatment) based on ISIS 420915 Enrolled Patients, ISIS 420915 ECHO Subgroup, and ISIS 420915 CM-ECHO Set
- mNIS+7 Composite Score: Response Rate by Threshold Value by Visit (On-Treatment) based on ISIS 420915 FAS

- Summary of PND Score Shift from Baseline by Visit (On-Treatment) based on ISIS 420915 FAS
- Summary of PND Score Change from Baseline by Visit (On-Treatment) based on ISIS 420915 FAS
- Summary of Select Questions from NSC (On-Treatment) and (Post-Treament) based on ISIS 420915 FAS

9.2.2.4 PK and IM Analyses

- Summary of ISIS 420915 Trough Plasma Concentrations (ng/mL) (On-Study) based on ISIS 420915 PK Set
- Summary of ISIS 420915 Trough Plasma Concentrations (ng/mL) (On-Study) by IM based on ISIS 420915 PK Set
- Incidence and Incidence Rate of Sample Immunogenicity Status (On-Study) based on ISIS 420915 Safety Set
- Summary of Anti-ISIS 420915 Antibody Titer Values over Time (On-Study) based on ISIS 420915 Safety Set
- Incidence and Incidence Rate of Subject Immunogenicity Status (On-Study) based on ISIS 420915 Safety Set
- Summary Statistics of Onset and Peak Titer of the ADA Response by Treatment in Patients with Positive Patients Immunogenicity Status (On-Study) based on ISIS 420915 Safety Set
-

9.2.2.5 Patient Characteristics and Population

- Summary of Treatment Discontinuations and Study Withdrawals Associated with COVID-19 Based on ISIS 420915 Treated Set
- Summary of Patients with Protocol Deviations Based on ISIS 420915 Treated Set
- Summary of Patients with Protocol Deviations Associated with COVID-19 Based on ISIS 420915 Treated Set
- Summary of Analysis Populations Based on ISIS 420915 Treated Set
- Summary of Concomitant Medications based on ISIS 420915 Safety Set

9.2.2.6 ECG QRS Analyses

- Number and percent patient who have post baseline QRS value >160ms and 25% of CS2 Baseline based on CS2 Safety Set
- Number and percent patient who have post baseline QRS value >160ms and 25% of CS2 or CS3 Baseline based on CS3 Safety Set

- Number and percent patient who have post baseline QRS value >160ms and 25% of ISIS 420915 Baseline based on ISIS 420915 Safety Set