A Phase 3 Global, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of ION-682884 in Patients With Hereditary Transthyretin-Mediated Amyloid Polyneuropathy

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Summary of Clinical Study Results

NEURO-TTRansform: A Study to Evaluate the Efficacy and Safety of Eplontersen (Formerly Known as ION-682884, IONIS-TTR-L_{Rx} and AKCEA-TTR-L_{Rx}) in Participants With Hereditary Transthyretin-Mediated Amyloid Polyneuropathy

Protocol #: ION-682884-CS3
Study dates: December 2019 to July 2023

Thank you to the participants who took part in the study, "A Study to Evaluate the Efficacy and Safety of Eplontersen (Formerly Known as ION-682884, IONIS-TTR-L_{Rx} and AKCEA-TTR-L_{Rx})", also known as the NEURO-TTRansform study.

Why was this study done?

Hereditary transthyretin (hATTR) amyloidosis is an uncommon and not well-known disease that gets worse quickly, cannot be reversed and if not treated can be deadly. hATTR is caused by changes in a specific gene that makes a protein called transthyretin (TTR). Genes are pieces of DNA that provide instructions to make a specific type of genetic material called messenger ribonucleic acid (mRNA), which is like a recipe for making proteins in the body. Genetic diseases are passed on from parents to children through altered (mutated) genes. In hATTR, these mutated genes can lead to unstable TTR proteins that break apart into smaller parts and can form clumps called amyloid fibrils. These clumps build up in various tissues in the body. When the build-up happens in nerves (units like wires that send messages between the brain and the body), the nerves become damaged. Damaged nerves can cause problems with movement, loss of feeling (numbness) in the arms and legs (sensorimotor neuropathy) and affect bodily functions like digestion (the process your body uses to break down the food you eat into smaller parts) and urination (how your body removes liquid waste; peeing). People have different presentations of hATTR. The type of hATTR presentation that affects the nerves, digestion, and urination is called hATTR with polyneuropathy (hATTR-PN). Between 10,000 and 50,000 people worldwide are suffering from hATTR-PN. After being diagnosed with hATTR-PN, people who are untreated usually live for about 5 to 15 more years.

In this study, researchers looked at a potential new medicine called eplontersen. Eplontersen is an antisense oligonucleotide (ASO), a type of medicine that attaches itself to hATTR mRNA. When eplontersen attaches to the mRNA for TTR protein, it causes the mRNA to break down. Breaking down mRNA means that less of the unstable protein is made. As a result, the cells (the smallest units of any living thing; the building blocks of life) in the body make less of the damaging TTR protein, which

can be helpful for people with hATTR-PN to better manage their disease. Eplontersen combines the ASO part of the medicine with a substance called triantennary N-acetyl galactosamine (GalNAc) to make a combined ASO-GalNAc medicine. This ASO-GalNAc combination helps the ASO medicine get taken up better by the liver, which is where the TTR protein is made before it is circulated throughout the body. Targeting the GalNAc-ASO to liver cells brings the medicine to those cells in the body where TTR protein is created and where it is most needed.

This study helped researchers find out if the medicine called eplontersen lowered the TTR protein, was safe and improved the quality of life for people with hereditary transthyretin-mediated amyloid polyneuropathy (hATTR-PN).

When was this study done?

This study started in December 2019 and ended in July 2023.

Who took part in this study?

People could take part in the study if they fit the following criteria:

- Were at least 18 years old, but not older than 82 years
- Used highly effective contraception (birth control) methods or were abstinent (not have sex) during the course of the study
- Had been diagnosed with hATTR-PN
- Willing to take vitamin A supplements

People could not take part in the study if they fit the following criteria:

- Had any important issues found in medical history, laboratory tests, or physical examinations that could make them unsuitable to take part in the study
- Had been diagnosed with other types of amyloidosis (amyloidosis has other causes, for example mutations in genes other than hATTR)
- Had other conditions that the researchers believed would interfere with the study

For more information on who could take part in this study, please refer to the websites listed at the end of this summary.

How many people took part in this study?

Overall, 168 people took part in this study (participants), of whom 116 (69%) were men and 52 (31%) were women.

The study took place at 40 clinics in Argentina, Australia, Brazil, Canada, Cyprus, France, Germany, Italy, New Zealand, Portugal, Spain, Sweden, Taiwan, Turkey, and the United States.

- 26 participants (15%) enrolled in North America
- 64 participants (38%) enrolled in Europe
- 78 participants (46%) enrolled in South America, Australasia/Asia

What happened during the study?

What did researchers want to know?

The main goal of the NEURO-TTRansform study was to see how well eplontersen worked in adult participants with hATTR-PN compared with participants who received placebo in a previous study called NEURO-TTR, which compared inotersen treatment against placebo in participants with ATTRv-PN. Inotersen is a different ASO medicine similar to eplontersen, but is not the same, and is not targeted to liver cells. In addition, a small group of participants were treated with inotersen until Week 35 of the study and then switched to receiving eplontersen. A placebo is an inactive substance that looks like and is administered as the study medicine but does not actually contain any medicine.

The main questions researchers wanted to answer in this study were the following:

- **Does eplontersen change the levels of TTR in the blood?**
- **Does eplontersen help improve the symptoms of nerve damage in adults with hATTR-PN?**

To address these questions, participants were given injections of eplontersen under the skin every 4 weeks until the final dose at week 81. Participants could receive their treatment at the study center or do it at home by themselves or with the help of a caregiver or home healthcare provider. Regardless of the treatment they received, all participants were required to take vitamin A supplements every day.

What treatments were studied?

- Eplontersen, 45 milligrams (mg), given every 4 weeks as an injection under the skin (subcutaneous) from Day 1 to Week 81.
- Inotersen, 300 milligrams (mg), given every week as an injection under the skin (subcutaneous) from weeks 1-34 and then eplontersen, 45 mg, from Week 37 to 81.

How was the study done?

There are many types of clinical studies. This study can be described as follows:

- Phase 3: This phase is usually the last phase of clinical research before a new medicine is submitted to government authorities for marketing approval. A study at this phase is used to confirm the effect of a medicine (how well it works) and learn more about the medicine's safety (side effects from the medicine) and tolerability (side effects from medicine after repeated use).
- Randomized: Who got eplontersen versus inotersen was decided randomly by a computer program.

- Open label: A type of research study where both the researchers and the participants know which treatment is being given.

Before the study began, all participants were screened (evaluated) to be sure they were a good fit for the study.

Screening Period

- During the screening period, participants provided their written consent (agreement) to how the study would be done (the study procedures) and underwent a review process to determine whether they were eligible to participate in the study, including completing a physical exam, answering questions about their medical and disease history, and providing blood and urine for samples for laboratory testing.
- The screening period lasted up to 10 weeks.

Treatment Period

- Following the screening period, participants were randomly assigned (meaning assigned by chance by a computer program) to receive either eplontersen or inotersen in a ratio of 6 participants to receive eplontersen for every 1 person to receive inotersen. This arrangement ensured a balanced assignment of participants to each group.
- Participants in the eplontersen group received 45 mg of eplontersen injected under the skin once every 4 weeks for up to 81 weeks.
- Participants in the inotersen group first received 300 mg of inotersen injected under the skin once a week for up to 34 weeks, then switched to receiving 45 mg of eplontersen injected under the skin once every 4 weeks from week 37 to week 81.
- Throughout the study, all participants were given daily vitamin A supplements.
- The treatment period lasted for 84 weeks (a little over 1 and a half years).

Follow-up Period

- After ending their treatment, participants who were eligible had the option to join a long-term extension study (ION-682884-CS13) where they would continue to receive eplontersen every 4 weeks.
- The long-term extension study allowed researchers to collect more information on the safety and effectiveness of eplontersen.
- Participants who did not move on to the long-term extension study entered a 20-week follow-up period after the last dose to monitor for side effects (safety).

Throughout the study, all participants had a minimum of 11 visits to the study site starting from Week 1. During these visits, participants had various tests done, including checking platelet count, kidney function, urine protein levels, and liver function. Some participants also had extra blood samples taken to assess how the medicine was being processed by the body.

What were the results of the study?

Out of the 144 participants who were in the eplontersen group, 135 (94.4%) reached week 66 of the study. Out of the 24 participants in the inotersen group, 20 (83.3%) reached week 66.

The information that was collected (data) showed that eplontersen worked better compared to historical placebo for lowering the amount of TTR protein in the blood. The reduction in TTR protein was about 82% for the eplontersen group and about 11% in the historical placebo group from the NEURO-TTR study. The data also showed that nerve damage in participants who received eplontersen was halted and participants had improved wellbeing (quality of life) when compared with the historical placebo group. Nerve damage was measured by the modified neuropathy impairment score plus seven (mNIS+7) test and quality of life (QOL) was measured by participants completing the Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) questionnaire. The Norfolk QoL-DN includes questions for the person to answer about various aspects of their daily life, such as how well they could perform basic daily activities, the state of their emotional well-being, and their experiences with social activities.

The positive effects seen in participants treated with eplontersen continued through the end of the study.

What medicine-related side effects did participants have during the study?

A summary of the medicine-related side effects that happened during the study is shown below. Not all participants had side effects. Side effects are undesirable experiences associated with the use of a medicine.

A side effect is called serious when it results in death, is life-threatening, causes lasting problems, or requires hospital care.

- Total amount of participants that participated in the study: 168
- 140 out of 144 participants (97%) in the eplontersen group compared with 60 out of 60 participants (100%) in the historical placebo group had treatment emergent side effects.
- 21 out of 144 participants (15%) in the eplontersen group compared with 12 out of 60 participants (20%) in the historical placebo group had serious treatment emergent side effects.
- 8 out of 144 participants (5%) in the eplontersen group compared with 2 out of 60 participants (3%) stopped treatment with study drug due to side effects.
- 3 participants in the eplontersen group died during the study. Their doctors considered their deaths to not be due to eplontersen.

The most common side effects that were reported in at least 10% of participants treated with eplontersen were the following:

Commonly Reported Side Effects		
Side Effect Reported	**Eplontersen Group (144 participants)**	**Historical Placebo Group (60 participants)**
Urinary tract infection	28 out of 144 participants (19%)	11 out of 60 participants (18%)
COVID-19	48 out of 144 participants (33%)	0[a]
Diarrhoea	28 out of 144 participants (19%)	12 out of 60 participants (20%)
Nausea	16 out of 144 participants (11%)	7 out of 60 participants (12%)
Vitamin A deficiency	17 out of 144 participants (12%)	0[b]

a = before the COVID-19 pandemic

b = no side effects were reported because Vitamin A test results were blinded in the NEURO-TTR study. Blinding means keeping certain information secret from either the participants, the researchers, or both- like a blindfold in a game, where you cannot see what is happening. Blinding helps make sure that the results of the study are as fair and accurate as possible.

For more information on the study results, refer to the websites listed at the end of this summary.

How has this study helped participants and researchers?

Overall, researchers learned that participants who received treatment with eplontersen showed improvements in their condition. Specifically, participants had significantly lower levels of the TTR protein in their blood, their symptoms of hATTR-PN did not progress, and they reported improved quality of life compared with those who had received a placebo in a previous study.

Findings from this study may be used in other studies to learn more about the use of eplontersen in people with hATTR.

Are there plans for further studies?

Further clinical studies with eplontersen are ongoing at this time that can be helpful for other conditions.

Where can I find out more about this study?

- Official Title of this Study: A Phase 3 Global, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of ION-682884 in Patients With Hereditary Transthyretin-Mediated Amyloid Polyneuropathy

- Protocol Number: ION-682884-CS3
- EU Study Number: 2019-001698-10

Clinical Trials register - Search for 2019-001698-10

- US Study Number: NCT04136184

https://clinicaltrials.gov/study/NCT04136184

- Journal of the American Medical Association (JAMA) Publication

Coelho T, Marques W Jr, Dasgupta NR, et al. Eplontersen for Hereditary Transthyretin Amyloidosis With Polyneuropathy. *JAMA*. 2023;330(15):1448-1458. doi:10.1001/jama.2023.18688

IONIS PHARMACEUTICALS, INC.

ION-682884-CS3

A Phase 3 Global, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of ION-682884 in Patients with Hereditary Transthyretin-Mediated Amyloid Polyneuropathy

Amendment 5 – 12 August 2021

EudraCT No: 2019-001698-10

NEURO - TTRANSFORM

Strategy to Improve Patient Outcomes by Silencing TTR Formation in hATTR-PN

Trial Sponsor	Ionis Pharmaceuticals 2855 Gazelle Court Carlsbad, CA 92010 Telephone Number: +01 760 931 9200 Fax Number: +01 760 603 2700
Key Sponsor Contact	[redacted]
Date	12 August 2021

ION-682884-CS3

Amendment 5

EudraCT No: 2019-001698-10

Clinical Phase: 3

A Phase 3 Global, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of ION-682884 in Patients with Hereditary Transthyretin-Mediated Amyloid Polyneuropathy

Protocol History

Original Protocol:	28 June 2019
Amendment 1:	6 August 2019
Amendment 2	18 September 2019
Amendment 3	30 January 2020
Amendment 4:	11 December 2020

NEURO – TTRANSFORM

Strategy to Improve Patient Outcomes by Silencing TTR Formation in hATTR-PN

Sponsor
Ionis Pharmaceuticals, Inc.
Carlsbad, CA 92010

[redacted]

Confidentiality Statement

Protocol Signature Page

Protocol Number:	ION-682884-CS3
Protocol Title:	A Phase 3 Global, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of ION-682884 in Patients with Hereditary Transthyretin-Mediated Amyloid Polyneuropathy
Amendment:	Amendment 5
Date:	12 August 2021

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "A Phase 3 Global, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of ION-682884 in Patients with Hereditary Transthyretin-Mediated Amyloid Polyneuropathy", dated12 August 2021, and agree to conduct the study as described herein.

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

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

Investigator's Signature

Investigator's Name *(please print)* Date (DD Month YYYY)

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PROTOCOL AMENDMENT

Protocol Number:	ION-682884-CS3
Protocol Title:	A Phase 3 Global, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of ION-682884 in Patients with Hereditary Transthyretin-Mediated Amyloid Polyneuropathy
Amendment:	Amendment 5
Date:	12 August 2021

This protocol amendment presents updates in comparison with ION-682884-CS3 Protocol Amendment , dated 11 December 2020.

The main purpose of this amendment is to update the frequency of safety monitoring of platelet count, eGFR and UPCR, [redacted]

Minor changes (not included in the list of changes below) have also 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 body. Protocol Synopsis and the table of Schedule of Assessments in Appendix A are updated accordingly.

Protocol Sections	Description of Modification	Rationale
Synopsis Section 5.2 Exclusion Criteria	**Was:** 9. Previous treatment with Tegsedi™ (inotersen) or Onpattro™ (patisiran) or other oligonucleotide or RNA therapeutic (including siRNA). **Is:** 9. Current or previous treatment with Tegsedi™ (inotersen) or Onpattro™ (patisiran) or other oligonucleotide or RNA therapeutic (including siRNA). This exclusion criterion does not apply to COVID-19 mRNA vaccinations.	Updated to clarify that this Exclusion Criterion does not apply to COVID-19 mRNA vaccines

Protocol Sections	Description of Modification	Rationale
Section 6.1.3 Treatment Period	**Was:** During Study Week 1, patients will report to the Study Center for evaluations and ION-682884 or inotersen administration on Day 1. After Week 1, ION-682884 will be administered once every 4 weeks. Inotersen will be administered once weekly. There will be a total of 43 visits [11 mandatory in-clinic visits and 32 visits that can be completed in-clinic, at home by a home health-care provider (if approved locally), or using a laboratory local to the patient upon Investigator approval] during Weeks 1-83 for study procedures and ION-682884 or inotersen administration (see Schedule of Procedures in Appendix A). **Is:** During Study Week 1, patients will report to the Study Center for evaluations and ION-682884 or inotersen administration on Day 1. After Week 1, ION-682884 will be administered once every 4 weeks through the end of the Treatment Period. Inotersen will be administered once weekly up to and including Week 34 at which time patients will transition to every 4 week administration of ION-682884. For patients randomized to the ION-682884 treatment arm, there will be a total of 43 visits during Weeks 1-83 for ION-682884 administration and other study procedures (see Schedule of Procedures in Appendix A). Eleven of the 43 visits are mandatory in-clinic visits, whereas 32 visits can be completed either in-clinic, at home by a home health-care provider (if approved locally), or by using a local laboratory upon Investigator approval.	Updated to reflect the different safety monitoring frequency for patients receiving ION-682884 and inotersen

Protocol Sections	Description of Modification	Rationale
Section 6.1.3 Treatment Period	For patients randomized to the inotersen reference arm, there will be a total of 60 visits during Weeks 1-83 for Study Drug administration and other study procedures (see Schedule of Procedures in Appendix A). Eleven of the 60 visits are mandatory in-clinic visits, whereas 49 visits can be completed either in-clinic, at home by a home health-care provider (if approved locally), or by using a local laboratory upon Investigator approval.	Updated to reflect the different safety monitoring frequency for patients receiving ION-682884 and inotersen
Section 6.1.3 Treatment Period	**Was:** During the Treatment Period, frequency of sample collection for hematology, chemistry and urinalysis will be once every 2 weeks for all patients. The window for blood collections that occur outside clinic visits is ± 4 days. See Section 8.5 for guidance on ION-682884 or inotersen dosing relative to hematology and chemistry monitoring. **Is:** Patients randomized to the ION-682884 treatment arm will have their platelet count, eGFR, UPCR, and LFTs assessed once every 4 weeks during the Treatment Period. Patients randomized to the inotersen reference arm will have their platelet count, eGFR, UPCR, and LFTs assessed every 2 weeks during the Treatment Period up to and including Week 34. After Week 34, patients assigned to the inotersen reference arm will transition to receive ION-682884 through the end of the Treatment Period. After patients in the inotersen reference arm transition to ION-682884, they will continue to have every 2-week platelet count, eGFR, UPCR, and LFTs measurements for 8 weeks after their last dose of inotersen. They will then be assessed every 4 weeks for platelet count, eGFR, UPCR, and LFTs through the end of the Treatment Period.	Updated to reflect the different safety monitoring frequency for patients receiving ION-682884 and inotersen

Protocol Sections	Description of Modification	Rationale
Section 8.5 Safety Monitoring Rules	**Was:** • The average of all non-missing pre-dose assessments. The window for blood collections (hematology and chemistry) that occur outside clinic visits is ± 4 days. **Is:** • Average of the pre-dose test closest to Day 1 and Day 1. The window for blood collections (hematology and chemistry) that occur outside clinic visits is ± 4 days.	Updated to align with the Statistical Analysis Plan
Section 8.5.1 Safety Monitoring Rules for Liver Chemistry Tests	**Was:** The following rules are adapted from the draft guidance for industry, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," issued by the U.S. Department of Health and Human Services, Food and Drug Administration, July 2009. For a definition of Baseline, please refer to guidance in Section 8.5 above. In the event of an ALT or AST measurement that is > 3 × ULN (or 2 × Baseline value if the Baseline value was > ULN) at any time during the study (Treatment or Post-Treatment Period), repeat testing should be performed within 48 to 72 hours of liver chemistry tests (ALT, AST, ALP, total bilirubin and international normalized ratio [INR]) to confirm the abnormalities and to determine if they are increasing or decreasing. There also should be inquiry made about symptoms. Additional, confirmatory measurements should also be performed if ALT or AST levels increase to 5 × ULN. **Is:** The following rules are adapted from the draft guidance for industry, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," issued by the U.S. Department of Health and Human Services, Food and Drug Administration, July 2009. For a definition of Baseline, please refer to guidance in Section 8.5 above. Monitoring frequency will be once every 4 weeks in patients randomized to the ION-682884 treatment arm until the end of the Treatment Period. Patients randomized to the inotersen reference arm will have their liver chemistry assessed every 2 weeks during the Treatment Period up to and including Week 34.	Updated to reflect the different safety monitoring frequency for patients receiving ION-682884 and inotersen

Protocol Sections	Description of Modification	Rationale
Section 8.5.1 Safety Monitoring Rules for Liver Chemistry Tests (Continued)	After patients in the inotersen reference arm transition to ION-682884 they will continue to have every 2 week liver chemistry measurements for 8 weeks after their last dose of inotersen. They will then be assessed every 4 weeks, through the end of the Treatment Period. For inotersen patients who terminate treatment before the end of the Treatment Period, liver chemistry measurements should be monitored once every 2 weeks, for a duration of 8 weeks. In the event of an ALT or AST measurement that is > 3 × ULN (or 2 × Baseline value if the Baseline value was > ULN) at any time during the study (Treatment or Post-Treatment Period), repeat testing should be performed within 48 to 72 hours of liver chemistry tests (ALT, AST, ALP, total bilirubin and international normalized ratio [INR]) to confirm the abnormalities and to determine if they are increasing or decreasing. There also should be inquiry made about symptoms. Additional, confirmatory measurements should also be performed if ALT or AST levels increase to 5 × ULN.	

Protocol Sections	Description of Modification	Rationale
Section 8.5.2 Safety Monitoring for Renal Function	**Was:** Serum creatinine, estimated glomerular filtration rate (eGFRcreat-cys, calculated using the CKD EPI creatinine-cystatin C equation [2012]), urinalysis, and UPCR should be monitored every 2 weeks in all patients taking ION-682884 or inotersen. In the event of a confirmed (as described in Section 8.5) laboratory result meeting 1 or more of the following criteria: **Is:** Serum creatinine, estimated glomerular filtration rate (eGFRcreat-cys, calculated using the CKD-EPI creatinine-cystatin C equation [2012]), urinalysis, and UPCR should be monitored every 4 weeks in all patients randomized to the ION-682884 treatment arm and every 2 weeks in all patients randomized to the inotersen reference arm, up to and including Week 34. After Week 34, patients assigned to the inotersen reference arm will transition to receive ION-682884 through the end of the Treatment Period. After patients in the inotersen reference arm transition to ION-682884, they will continue to have every 2-week measurements for 8 weeks after their last dose of inotersen. They will then be assessed every 4 weeks through the end of the Treatment Period.. For inotersen patients who terminate treatment before the end of the Treatment Period, renal function should be monitored once every 2 weeks, for a duration of 8 weeks..	Updated to reflect the different safety monitoring frequency for patients receiving ION-682884 and inotersen

Protocol Sections	Description of Modification	Rationale
Section 8.5.3 Safety Monitoring Rules for Platelet Count Results	**Was:** Platelet monitoring will be every 2 weeks in all patients taking ION-682884 and inotersen until the end of the Treatment Period. For patients who terminate treatment before the end of the Treatment Period, platelets should be monitored once every 2 weeks, for a duration of 8 weeks for both treatment arms. **Is:** Platelet count monitoring frequency will be once every 4 weeks in patients randomized to the ION-682884 treatment arm until the end of the Treatment Period. Patients randomized to the inotersen reference arm will have their platelet count assessed every 2 weeks during the Treatment Period up to and including Week 34. After Week 34, patients assigned to the inotersen reference arm will transition to receive ION-682884 through the end of the Treatment Period. After patients in the inotersen reference arm transition to ION-682884, they will continue to have every 2-week platelet count measurements for 8 weeks after their last dose of inotersen. They will then be assessed every 4 weeks for platelet count through the end of the Treatment Period. For inotersen patients who terminate treatment before the end of the Treatment Period, platelets should be monitored once every 2 weeks, for a duration of 8 weeks.	Updated to reflect the different safety monitoring frequency for patients receiving ION-682884 and inotersen
Table 4: Actions in Patients with Low Platelet Count	Table updated to differentiate between the action to be taken for patients receiving ION-682884 verses patients receiving inotersen	Updated to reflect the different safety monitoring frequency for patients receiving ION-682884 and inotersen
Appendix A Schedule of Procedures	Updated the frequency of safety monitoring to every 4 weeks for patients receiving ION-682884.	Updated to reflect the different safety monitoring frequency for patients receiving ION-682884 and inotersen

PROTOCOL SYNOPSIS

Protocol Title	A Phase 3 Global, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of ION-682884 in Patients with Hereditary Transthyretin-Mediated Amyloid Polyneuropathy
Study Phase	3
Indication	Hereditary transthyretin-mediated amyloid polyneuropathy (hATTR-PN)
Primary Objective	To evaluate the efficacy of ION-682884, based on the change from Baseline in serum Transthyretin (TTR) concentration, modified Neuropathy Impairment Score +7 (mNIS+7), and Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QOL-DN) as compared to the historical control of placebo arm in the ISIS 420915-CS2 NEURO-TTR (inotersen) trial
Secondary Objectives	To evaluate the efficacy of ION-682884, as compared to the placebo cohort in the NEURO-TTR trial, based on the change from Baseline in: • Neuropathy Symptom and Change (NCS) score • Physical Component Summary (PCS) score of 36-Item Short Form Survey (SF-36) • Polyneuropathy disability (PND) score • Modified body mass index (mBMI)
Additional/ Exploratory Objectives	To evaluate the efficacy of ION-682884 in mNIS+7 at Week 85, compared to Baseline. To evaluate the efficacy of ION-682884 in the Change from Baseline in the Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) at Weeks 37 and 85. To evaluate the efficacy of ION-682884, as compared to the historical control of the placebo arm in the ALN-TTR02-004 trial (APOLLO trial, ClinicalTrials.gov Identifier: NCT01960348) in: • Change from Baseline in Norfolk QOL-DN at Week 85 • Change from Baseline in 10-Meter Walk Test (10MWT) • Change from Baseline in Rasch-built Overall Disability Score (R-ODS) • Change from Baseline in Composite Autonomic Symptom Score-31 (COMPASS-31) • Change from Baseline in 5 Level EQ-5D (EQ-5D-5L) To evaluate the efficacy of ION-682884, as compared to the placebo cohort in the NEURO-TTR trial, in: • Change from Baseline in the SF-36 • Frequency of all-cause hospitalizations (in all patients and in patients with cardiac involvement) • Change from Baseline in transthoracic echocardiogram (ECHO) parameters including left ventricular (LV) mass, LV wall thickness, intraventricular septum (IVS) thickness, global longitudinal strain (GLS), in patients with cardiac involvement

PROTOCOL SYNOPSIS CONTINUED

Additional/ Exploratory Objectives Continued	• Change from Baseline in N-terminal pro b-type natriuretic peptide (NT-proBNP) in patients with cardiac involvement To evaluate the plasma trough and post-treatment concentrations of ION-682884 or inotersen in all patients, and to evaluate plasma pharmacokinetic (PK) parameters in a subset of patients.
Safety Objectives	To evaluate safety and tolerability of ION-682884 in hATTR-PN patients, in the following measures: change from Baseline in platelet count and renal function, adverse events, vital signs and weight, physical examination findings, clinical laboratory tests, electrocardiogram (ECG) parameters, use of concomitant medication, thyroid panel tests, inflammatory panel tests, coagulation tests, and immunogenicity tests.
Study Design	This is a multicenter, open-label study with historical controls and an active reference arm (inotersen). Approximately 140 patients will be randomized 6:1 to receive subcutaneous (SC) injections of either ION-682884 [redacted] once every 4 weeks or inotersen [redacted] once a week. Patients will also take daily supplemental doses of the recommended daily allowance of vitamin A. An interim analysis will be conducted at Week 35. Primary endpoint (PEP) analysis will be performed at Week 66. Patients included in the inotersen reference arm will be crossed over to ION-682884 at Week 37 after completing the Week 35 assessments. All patients will continue dosing with ION-682884 until Week 81 with end-of-treatment (EOT) assessments at Week 85, 4 weeks after the last dose. At Week 35, an interim analysis will be performed in hierarchical order for the following 3 efficacy endpoints: 1) serum TTR reduction; 2) mNIS+7; 3) Norfolk QOL-DN. At Week 66, co-primary endpoints will be: 1) serum TTR reduction; 2) mNIS+7; 3) Norfolk QOL-DN. Following treatment and the EOT assessments, eligible patients may elect to enroll in an open-label extension (OLE) study pending study approval by the Institutional Review Board/Independent Ethics Committee (IRB/IEC) and the appropriate regulatory authorities. All participating patients in the OLE study will continue to receive ION-682884 once every 4 weeks. Patients not participating in the OLE will enter the 20-week post-treatment evaluation portion of this study after completing the EOT assessments. A Data and Safety Monitoring Board (DSMB) will be established to review safety, tolerability and efficacy data (as needed) collected during this study, both individual events and aggregate data.

PROTOCOL SYNOPSIS CONTINUED

Number of Patients	Approximately 140 patients will be enrolled into this study
Study Population	To be eligible to participate in this study candidates must meet the following eligibility criteria within 10 weeks of Study Day 1, or at the time point specified in the individual eligibility criterion listed. The Sponsor Medical Monitor may be consulted if any questions arise regarding the inclusion or exclusion criteria. **Inclusion Criteria** 1. Must have given written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements 2. Aged 18 to 82 years at the time of informed consent 3. Satisfy the following: a. Females: must be non-pregnant and non-lactating and either: i. Surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) ii. Post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved) iii. Abstinent* or iv. If engaged in sexual relations of child-bearing potential, agree to use highly effective contraceptive methods (refer to Section 6.3.1) from the time of signing the informed consent form until at least 24 weeks after the last dose of ION-682884 or inotersen and agree to receive a monthly pregnancy test b. Males: Surgically sterile (i.e., bilateral orchidectomy) or, if engaged in sexual relations with a woman of child-bearing potential (WOCBP), the patient or the patient's non-pregnant female partner must use a highly effective contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 24 weeks after the last dose of ION-682884 or inotersen. * Abstinence (i.e., refraining from heterosexual intercourse throughout the duration of study participation) is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception.

PROTOCOL SYNOPSIS CONTINUED

Study Population Continued	**Inclusion Criteria Continued** 4. hATTR-PN as defined by meeting all 3 of the following criteria: a. Stage 1 (ambulatory without assistance) or Stage 2 (ambulatory with assistance) according to the Familial Amyloid Polyneuropathy (FAP) or Coutinho Stage b. Documented genetic mutation in the TTR gene c. Symptoms and signs consistent with neuropathy associated with transthyretin amyloidosis, including NIS ≥ 10 and ≤ 130 5. Willingness to adhere to vitamin A supplementation per protocol **Exclusion Criteria** 1. Clinically significant abnormalities in medical history (e.g., previous acute coronary syndrome within 6 months of Screening, major surgery within 3 months of Screening) or physical examination 2. Screening laboratory results as follows, or any other clinically significant abnormalities in screening laboratory values that would render a patient unsuitable for inclusion: a. Urine protein/creatinine ratio (UPCR) ≥ 1000 mg/g. In the event of UPCR above this threshold, eligibility may be confirmed by a repeat random urine test with UPCR < 1000 mg/g or a quantitative total urine protein measurement of < 1000 mg/24 hr b. Renal insufficiency as defined by estimated glomerular filtration rate ($eGFR_{creat-cys}$) < 45 mL/min/1.73 m^2 at Screening ($eGFR_{creat-cys}$ is calculated using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] creatinine-cystatin C equation from 2012) (Inker et al. 2012) c. Positive test for blood (including trace) on urinalysis that is subsequently confirmed with urine microscopy showing > 5 red blood cells per high power field and is related to glomerulopathies. In women, this exclusion criterion must be assessed outside of menstrual period. If in the opinion of the Investigator the hematuria is not considered related to glomerulopathies the patient may be considered eligible, pending proper follow-up and a discussion with the medical monitor. Patients with history of bladder cancer must have been treated with curative intent and have not presented recurrence within the prior 5 years. d. Alanine aminotransferase/ aspartate aminotransferase (ALT/AST) > 2 × upper limit of normal (ULN) e. Bilirubin ≥ 1.5 × ULN (patients with bilirubin ≥ 1.5 × ULN may be allowed on study if indirect bilirubin only is elevated, ALT/AST is not greater than the ULN and known to have Gilbert's disease) f. Platelets < 125 × 10^9/L g. HbA1C ≥ 7% h. Abnormal thyroid function tests with clinical significance per Investigator judgement

PROTOCOL SYNOPSIS CONTINUED

Study Population Continued	**Exclusion Criteria Continued** 3. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1 4. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator 5. Known history of or positive test for human immunodeficiency virus (as evidenced by positive tests for HIV antibody and HIV RNA), hepatitis C (as evidenced by positive tests for HCV antibody and HCV RNA) or hepatitis B (as evidenced by a positive test for hepatitis B surface antigen) 6. Uncontrolled hypertension (BP > 160/100 mm Hg) 7. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin, melanoma in situ, prostate carcinoma grade group 1, breast ductal carcinoma in situ, or carcinoma in situ of the cervix. Patients with a history of other malignancies who have been treated with curative intent and without recurrence within 5 years may also be eligible per Investigator judgement 8. Current treatment with any approved drug for hereditary TTR amyloidosis such as Vyndaqel® / Vyndamax™ (tafamidis), Tegsedi™ (inotersen), Onpattro™ (patisiran), off-label use of diflunisal, doxycycline or tauroursodeoxycholic acid (TUDCA). If previously treated with Vyndaqel® / Vyndamax™, diflunisal or doxycycline, and TUDCA, must have discontinued treatment at least 2 weeks prior to Study Day 1 9. Current or previous treatment with Tegsedi™ (inotersen) or Onpattro™ (patisiran) or other oligonucleotide or RNA therapeutic (including siRNA). This exclusion criterion does not apply to COVID-19 mRNA vaccinations. 10. Treatment with another investigational drug, biological agent, or device within 3 months of screening, or 5 half-lives of study agent, whichever is longer 11. History of bleeding, diathesis or coagulopathy (e.g., liver cirrhosis, hematologic malignancy, antiphospholipid antibody syndrome, congenital disorders such as hemophilia A, B, and Von Willebrand disease) 12. Recent history of, or current drug or alcohol abuse 13. Use of oral anticoagulants, unless the dose has been stable for 4 weeks prior to the first dose of ION-682884 or inotersen and regular clinical monitoring is performed 14. Karnofsky performance status ≤ 50%

PROTOCOL SYNOPSIS CONTINUED

Study Population Continued	**Exclusion Criteria Continued** 15. Other causes of sensorimotor or autonomic neuropathy (e.g., autoimmune disease, diabetic neuropathy) 16. Prior liver transplant or anticipated liver transplant within 1 year of Screening 17. New York Heart Association (NYHA) functional classification of ≥ 3 18. Known immunoglobulin light chain amyloidosis (AL amyloidosis) 19. Known leptomeningeal amyloidosis 20. Known multiple myeloma 21. Monoclonal gammopathy of undetermined significance (MGUS) and/or alterations in immunoglobulin free light chain (FLC) ratio unless fat, bone marrow, or heart biopsy confirming the absence of light chain and the presence of TTR protein by mass spectrometry or immunoelectron microscopy. For patients with chronic kidney disease (CKD) and without presence of monoclonal protein in blood and urine, the acceptable FLC ratio is 0.26–2.25. Results different from that may be discussed with local hematologist, Investigator and Medical Monitor if the risks associated with the biopsy outweigh the benefits. 22. Presence of known type 1 or type 2 diabetes mellitus 23. Anticipated survival less than 2 years 24. Have any other conditions, which, in the opinion of the Investigator would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the study
Treatment Groups	Patients will be randomized 6:1 to receive either ION-682884 or inotersen
ION-682884 / Inotersen Dosage and Administration	ION-682884 will be administered once every 4 weeks [redacted] as a SC injection. Inotersen will be administered once every week [redacted] as a SC injection.
Rationale for Dose and Schedule Selection	A dose of [redacted] ION-682884, administered once every 4 weeks, was selected based on the pharmacodynamics and safety analysis of the Phase 1 study, ION-682884-CS1. A dose [redacted] of inotersen, administered weekly, was administered in the NEURO-TTR trial.
Adjustment of Dose and/or Treatment Schedule	Dose adjustments, including dose interruptions, may be allowed for safety or tolerability.
Study Visit Schedule and Procedures	Detailed information regarding the study procedures are outlined in Section 6 and Appendix A and Appendix C. The study for an individual patient will generally consist of the following periods: • A ≤ 10-week Screening Period and Baseline/Day 1 • An 84-week Treatment Period • A 20-week Post-Treatment Evaluation Period

PROTOCOL SYNOPSIS CONTINUED

Study Visit Schedule and Procedures Continued	Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), adverse events, concomitant medication/procedure information, pharmacodynamic (PD) parameters (TTR), ION-682884 or inotersen plasma trough and post-treatment concentrations, and immunogenicity testing 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, Norfolk QOL-DN, mBMI/BMI, SF-36, R-ODS, EQ-5D-5L, COMPASS-31, 10-meter walk test, physical examination, PND score, and ECG. All patients will also have a transthoracic ECHO conducted at Baseline, Week 35, 66, 85 and 105. Furthermore, approximately 28 patients will have additional PK sampling at specified visits according to the schedule of procedures (Appendix A). ION-682884 or inotersen will be administered at the Study Center during scheduled clinic visits as outlined in the schedule of procedures (Appendix A). Otherwise, administration of ION-682884 or inotersen may be given by either the Study Center personnel or at home by the patient/caregiver/home health-care provider. Dosing instructions and training on injection technique will be provided to the patient/caregiver/ home health-care provider.
Primary Endpoints	Week 35 Interim Analysis: Change from Baseline in serum TTR concentration and the mNIS+7; Week 66 Final Analysis: Change from Baseline in serum TTR concentration, mNIS+7 and Norfolk QOL-DN
Secondary Endpoints	Week 35 Interim Analysis: • Change from Baseline in Norfolk QOL-DN Week 66 Final Analysis: • Change from Baseline in the NSC score at Weeks 35 and 66 • Change from Baseline in the PCS score of SF-36 at Week 65 • Change from Baseline in PND score at Week 65 • Change from Baseline in mBMI at Week 65
Additional/Exploratory Endpoints	Change from Baseline in mNIS+7 at Week 85 Change from Baseline in Norfolk QOL-DN at Week 85 Change from Baseline in 10MWT at Weeks 37 and 81 Change from Baseline in R-ODS at Weeks 37 and 81 Change from Baseline in COMPASS-31 at Weeks 37 and 81 Change from Baseline in EQ-5D-5L at Weeks 37 and 81 Change from Baseline in the SF-36 at Week 35 Frequency of all cause hospitalizations in all patients by Week 66 Frequency of all cause hospitalizations in patients with cardiac involvement by Week 66

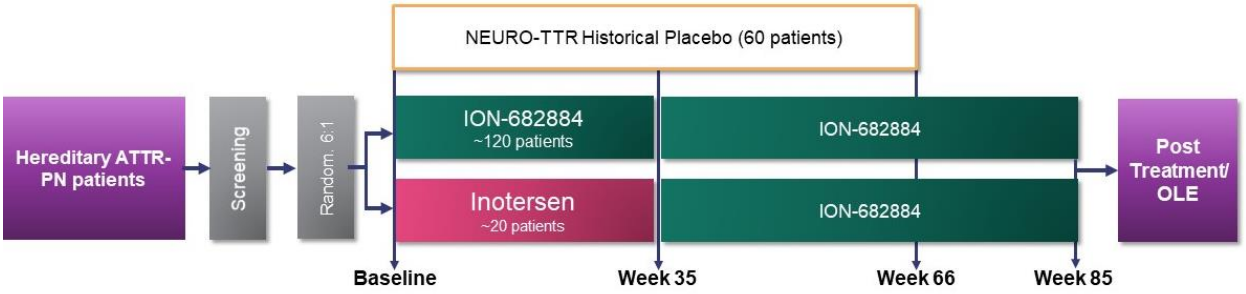
PROTOCOL SYNOPSIS CONTINUED

Additional/Exploratory Endpoints Continued	Change from Baseline in ECHO parameters, including LV mass, LV wall thickness, IVS thickness, and GLS, at Week 66 in patients with cardiac involvement Change from Baseline in NT-proBNP at Week 65 in patients with cardiac involvement Change from Baseline in PGIS at Weeks 37 and 85 PGIC at Weeks 37 and 85 Plasma trough and post-treatment concentrations of ION-682884 or inotersen in all patients, area under the curve (AUC), C_{max}, and T_{max} in a subset of patients, and $t_{½\lambda z}$ for patients who do not roll over to the OLE study.
Safety Endpoints	Change from Baseline in platelet count per Common Terminology Criteria for Adverse Events (CTCAE) grade. Change from Baseline in renal function. Additional safety endpoints include: adverse events, vital signs and weight, physical examination, clinical laboratory tests, ECG, use of concomitant medication, thyroid panel, inflammatory panel, coagulation, and immunogenicity.
Statistical Considerations	**Sample Size** The sample size for this study was estimated based on the data from the NEURO-TTR clinical trial. With 140 patients (120 of them dosed with ION-682884) and assuming a 10% dropout rate, there would be 108 evaluable patients treated with ION-682884. In the NEURO-TTR trial, there are 52 evaluable placebo patients. There would be at least 90% power to detect a 19.6 point difference in the change from Baseline of the mNIS+7 score between ION-682884-treated patients and the NEURO-TTR placebo patients, with a 2-sided alpha level of 0.025. For the serum TTR percent change from Baseline, there would be at least 95% power to detect a 70.3% difference in the percent change from Baseline between ION-682884-treated patients and the NEURO TTR-placebo patients, with a 2-sided alpha level of 0.025. **Week 35 Interim Analysis** The multiplicity will be controlled by using the ranking strategy in the following testing sequence: • Comparison of percent change from Baseline to Week 35 in serum TTR between ION-682884 and NEURO-TTR Placebo in the Full Analysis Set. • Comparison of change from Baseline to Week 35 in the mNIS+7 between ION-682884 and NEURO-TTR Placebo in the Full Analysis Set. • Comparison of change from Baseline to Week 35 in the Norfolk QOL-DN between ION-682884 and NEURO-TTR Placebo in the Full Analysis Set. The statistical analysis will be conducted with 2-sided alpha level of 0.025.

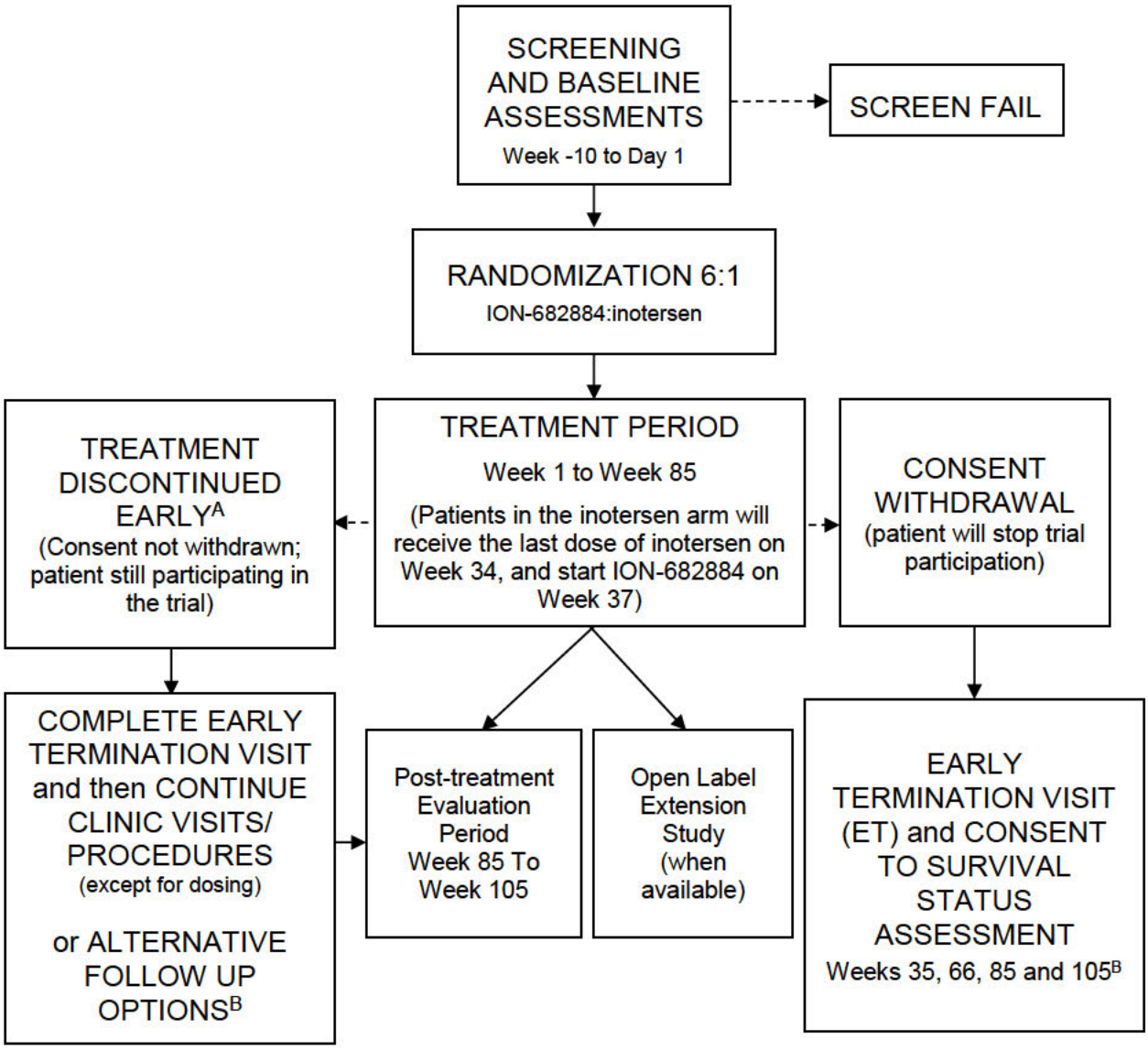
PROTOCOL SYNOPSIS CONTINUED

Statistical Considerations Continued	The percent change in serum TTR from Baseline to Week 35 will be analyzed using the Mixed Effects Model with Repeated Measures (MMRM) model adjusted by propensity score weights. **Week 35 Interim Analysis Continued** For mNIS+7 and Norfolk QOL-DN, the treatment comparison at Week 35 will be based on the ANCOVA model adjusted by propensity score. Patients with a missing mNIS+7 (or Norfolk QOL-DN) at Week 35 will have value multiply imputed using an imputation model. **Week 66 Final Analysis** The multiplicity for the final analysis will be controlled by using the ranking strategy in the following testing sequence: • Co-Primary Endpoint. Comparison of percent change from Baseline to Week 65 in serum TTR between ION-682884 and NEURO-TTR Placebo in the Full Analysis Set. • Co-Primary Endpoint. Comparison of change from Baseline to Week 66 in the mNIS+7 between ION-682884 and NEURO-TTR Placebo in the Full Analysis Set. • Co-Primary Endpoint. Comparison of change from Baseline to Week 66 in the Norfolk QOL-DN between ION-682884 and NEURO-TTR Placebo in the Full Analysis Set. • Secondary Endpoint: Comparison of change from Baseline to Week 66 in the NSC between ION-682884 and NEURO-TTR Placebo in the Full Analysis Set • Secondary Endpoint: Comparison of change from Baseline to Week 35 in the NSC between ION-682884 and NEURO-TTR Placebo in the Full Analysis Set • Secondary Endpoint: Comparison of change from Baseline in the PCS score of SF-36 at Week 65 between ION-682884 or NEURO-TTR Placebo in the Full Analysis Set • Secondary Endpoint: Comparison of change from Baseline to Week 65 in the PND between ION-682884 and NEURO-TTR Placebo in the Full Analysis Set. • Secondary Endpoint. Comparison of change from Baseline to Week 65 in mBMI between ION-682884 and NEURO-TTR Placebo in the Full Analysis Set In the Week 66 Final Analysis, the alpha level for this endpoint will be determined by the resampling procedure (Westfall and Young 1993). For those endpoints that are not tested in the interim analysis, significance level of 0.05 will be used. MMRM model adjusted by propensity score weights will be used for the primary and secondary analyses in the Week 66 Final Analysis. The reference arm with inotersen treatment will only be summarized descriptively
Sponsor	Ionis Pharmaceuticals

STUDY SCHEMA



SCHEMATIC PATIENT FLOW THROUGH THE STUDY



[A] Ideally, attempts need to be made to complete landmark visits (Weeks 35, 66, 85, and 105). Minimally, communication should be established with patients to obtain vital status at these visits.

[B] Status assessments and/or alternative follow up should be performed using the type of follow-up the patient is agreeable to: in person, by phone/mail, through family/friends, via correspondence/communication with other physicians, and/or from review of the medical records. The agreed means of follow-up will be documented in the patient records and notified to the Sponsor. However, if consent is withdrawn, patient will be removed from further treatment and study observation immediately upon the date of request.

STUDY GLOSSARY

Abbreviation	Definition
2′-MOE	2′-*O*-(2-methoxyethyl)
10MWT	10-Meter Walk Test
AE(s)	adverse event(s)
AESI	adverse events of special interest
AL amyloidosis	amyloid light amyloidosis
ALP	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
ANA	antinuclear antibody
aPTT	activated partial thromboplastin time
ASO(s)	antisense oligonucleotide(s)
AST	aspartate aminotransferase (SGOT)
AUC	area under the curve
Bb	complement factor Bb (activated complement split product)
βhCG	beta-subunit of human chorionic gonadotropin (pregnancy test)
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
C5a	complement factor C5a (activated complement split product)
C_{max}	maximum concentration
CBC	complete blood count
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMV	cytomegalovirus
COMPASS-31	Composite Autonomic Symptom Score-31
CRNMB	clinically relevant, non-major bleeding events
CTCAE	Common Terminology Criteria for Adverse Events
dL	deciliter
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
ECHO	echocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EOT	end-of-treatment
eGFR	estimated glomerular filtration rate
eplontersen	nonproprietary name for ION-682884
EQ-5D-5L	5-level EQ-5D version
FAP	familial amyloid polyneuropathy
FLC	free light chain
GCP	good clinical practice
GLS	global longitudinal strain
hATTR-PN	hereditary transthyretin-mediated amyloid polyneuropathy
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate

hsCRP	c-reactive protein measured by high sensitivity assay
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgM	immunoglobulin M
INR	international normalized ratio
ION-682884	Sponsor compound code for eplontersen (antisense inhibitor of transthyretin)
IRB	Institutional Review Board
ISIS-420915	antisense inhibitor of transthyretin with generic name of inotersen and brand name Tegsedi™
IUS	intrauterine hormone-releasing system
IV	intravenous(ly)
IVS	intraventricular septum
IXRS	Interactive Voice/Web-Response System
L	liter
LV	left ventricular
m^2	square meter
MB	major bleeding
mBMI	modified body mass index (defined as body mass index in kg/m^2 multiplied by serum albumin in g/L)
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA™	Medical Dictionary for Regulatory Activities
MGUS	monoclonal gammopathy of undetermined significance
MMRM	Mixed Effects Model with Repeated Measures
mNIS+7	modified neuropathy impairment score plus 7
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NCS	not clinically significant
Norfolk QOL-DN	Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (QOL-DN)
NSAID	non-steroidal anti-inflammatory drug
NSC	neuropathy symptom and change
NT-proBNP	N-terminal pro brain natriuretic peptide
NYHA	New York Heart Association
OLE	open-label extension
OLT	orthotopic liver transplant
on study	the patient is ‘on study’ from signing of the informed consent until their last study visit
PCS	physical component summary score
PD	pharmacodynamic
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PEP	primary endpoint
pH	measure of the acidity or basicity of a solution
PK	pharmacokinetic
PND	polyneuropathy disability score
PT	prothrombin time
QOL	quality of life
RBP4	retinol binding protein 4
RDA	recommended daily allowance

rINN	recommended international nonproprietary name
R-ODS	Rasch-built Overall Disability Score
RNase H1	an ubiquitous endonuclease that specifically hydrolyzes the RNA strand in RNA/DNA hybrids
SAE	serious adverse event
SAP	Statistical Analysis Plan
SF-36	36-Item Short Form Survey
siRNA	small interfering ribonucleic acid
SC	subcutaneous(ly)
Study Day 1	defined as the first day ION-682884 or inotersen is administered to the patient
SUSAR	suspected unexpected serious adverse reaction
TME(s)	targeted medical event(s)
t_{max}	time to maximal concentration
TUDCA	tauroursodeoxycholic acid
UACR	urine albumin to creatinine ratio
ULN	upper limit of normal
UPCR	urine protein to creatinine ratio
USAN	United States accepted name
VS	vital sign
WBC	white blood cell
WOCBP	woman of child-bearing potential

1. OBJECTIVES AND ENDPOINTS

1.1. Objectives

1.1.1. Primary Objectives

To evaluate the efficacy of ION-682884 after administration for 65 weeks, as compared to the historical control of the placebo cohort in the NEURO-TTR trial, based on the change from Baseline in serum TTR concentration, mNIS+7 and in the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QOL-DN) in patients with hATTR.

1.1.2. Secondary Objectives

To evaluate the efficacy of ION-682884, as compared to the placebo cohort in the NEURO-TTR trial, based on the change from Baseline in the following measures:

- Neuropathy Symptom and Change Score (NSC)
- Physical component summary (PCS) score of 36-Item Short Form Survey (SF-36)
- Polyneuropathy disability (PND) score
- Modified body mass index (mBMI)

1.1.3. Safety Objectives

To evaluate safety and tolerability in hATTR-PN patients treated with ION-682884 including the change from Baseline in platelet count and renal function, the presence of adverse events (AEs).

1.1.4. Additional/Exploratory Objectives

1.1.4.1. Efficacy Objectives

To evaluate the efficacy of ION-682884 in mNIS+7 at Week 85, compared to Baseline.

To evaluate the efficacy of ION-682884 in the Change from Baseline in the Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) at Weeks 37 and 85. To evaluate the efficacy of ION-682884, as compared to the historical control of the placebo arm included in the ALN-TTR02-004 (APOLLO trial, ClinicalTrials.gov Identifier: NCT01960348) in the following measures:

- Change from Baseline in Norfolk QOL-DN at Week 85
- Change from Baseline in 10-Meter Walk Test (10MWT)
- Change from Baseline in Rasch-built Overall Disability Score (R-ODS)
- Change from Baseline in Composite Autonomic Symptom Score-31 (COMPASS-31)
- Change from Baseline in 5-level EQ-5D version (EQ-5D-5L)

To evaluate the efficacy of ION-682884 as compared to the placebo cohort of the NEURO-TTR trial in:

- Change from Baseline in the SF-36
- Frequency of all-cause hospitalizations (in all patients and in patients with cardiac involvement)
- Change from Baseline in transthoracic echocardiogram (ECHO) parameters, including left ventricular (LV) mass, LV wall thickness, intraventricular septum (IVS) thickness, and global longitudinal strain (GLS), in patients with cardiac involvement
- Change from Baseline in N-terminal pro b-type natriuretic peptide (NT-proBNP) in patients with cardiac involvement

1.1.4.2. Pharmacokinetic Objectives

To evaluate the plasma trough and post-treatment concentrations of ION-682884 or inotersen in all patients, and to evaluate plasma pharmacokinetic (PK) parameters in a subset of patients.

1.2. Study Endpoints

1.2.1. Interim Analysis Co-Primary Efficacy Endpoints at Week 35

- Percent change from Baseline in serum TTR concentration at Week 35
- Change from Baseline in mNIS+7 at Week 35

1.2.2. Interim Analysis Key Secondary Efficacy Endpoint at Week 35

- Change from Baseline in Norfolk QOL-DN at Week 35

1.2.3. Final Analysis Co-Primary Efficacy Endpoints

- Percent change from Baseline in serum TTR concentration at Week 65
- Change from Baseline in mNIS+7 at Week 66
- Change from Baseline in Norfolk QOL-DN at Week 66

1.2.4. Final Analysis Secondary Endpoints

- Change from Baseline in NSC at Weeks 35 and 66
- Change from Baseline in the PCS score of SF-36 at Week 65
- Change from Baseline in PND score at Week 65
- Change from Baseline in mBMI at Week 65

1.2.5. Safety Endpoints

- Change from Baseline in platelet count during the Treatment Period
- Change from Baseline in renal function during the Treatment Period
- Adverse events
- Vital signs and weight
- Physical examination
- Clinical laboratory tests
- Electrocardiogram (ECG)
- Use of concomitant medication
- Thyroid panel
- Inflammatory panel
- Coagulation
- Immunogenicity

1.2.6. Additional/Exploratory Endpoints

1.2.6.1. Efficacy Endpoints

- Change from Baseline in mNIS+7 at Week 85
- Change from Baseline in Norfolk QOL-DN at Week 85
- Change from Baseline in 10MWT at Weeks 37 and 81
- Change from Baseline in R-ODS at Weeks 37 and 81
- Change from Baseline in COMPASS-31 at Weeks 37 and 81
- Change from Baseline in EQ-5D-5L at Weeks 37 and 81
- Change from Baseline in the SF-36 components at Weeks 35
- Frequency of all cause hospitalizations in all patients and in patients with cardiac involvement by Week 66
- Change from Baseline in transthoracic ECHO parameters, including LV mass, LV wall thickness, IVS thickness, and GLS, in patients with cardiac involvement at Week 66
- Change from Baseline in NT-proBNP in patients with cardiac involvement at Week 65
- Change from Baseline in PGIS at Weeks 37 and 85
- PGIC at Weeks 37 and 85

1.2.6.2. Pharmacokinetic Endpoints

Plasma trough and post-treatment concentrations of ION-682884 or inotersen in all patients, area under the curve (AUC), C_{max}, and T_{max} in a subset of patients, and $t_{½\lambda z}$ for patients who do not roll over to the open-label extension (OLE) study.

2. BACKGROUND AND RATIONALE

2.1. Overview of Disease

2.1.1. Disease Background

Hereditary transthyretin amyloidosis (hATTR) is a progressive, irreversible, and fatal disease caused by mutations in the gene that codes for transthyretin (TTR). Single-point gene mutations destabilize the normal TTR tetrameric structure, causing its dissociation into free monomers. These monomers misfold and subsequently aggregate into insoluble, extracellular fibril deposits, causing cell degeneration and death (Quintas et al. 2001; Plante-Bordeneuve and Said 2011). Accumulation of amyloid deposits in hATTR occur in multiple organ systems, including the peripheral nervous system, gastrointestinal tract, kidney, and heart. Due to the multiple organ deposition of amyloid, the disease has a wide spectrum of clinical manifestations. However, historically, hATTR has been divided into 2 major phenotypes: hATTR with polyneuropathy (hATTR-PN), and hATTR with cardiomyopathy (hATTR-CM).

The global prevalence of hATTR-PN has been estimated at approximately 10,000 patients (range 5,526–38,468) (Coelho et al. 2008; Schmidt et al. 2018). The main clinical manifestations of hATTR-PN is a progressive peripheral sensorimotor and autonomic neuropathy (Plante-Bordeneuve and Said 2011). Symmetrical loss of pain and temperature sensitivity typically begins in the lower extremities, progressing distal to proximal. Motor neuropathy follows within a few years, which affects ambulatory status (Coutinho et al. 1980; Sekijima et al. 2009; Plante-Bordeneuve and Said 2011). Hereditary ATTR-PN is classified into 3 stages (Familial Amyloid Polyneuropathy [FAP] or Coutinho Stages) based on ambulatory status (Coutinho et al. 1980): Stage 1 does not require assistance with ambulation, Stage 2 requires assistance with ambulation, and Stage 3 is wheelchair bound. This staging system was used to classify severity of disease in patients being considered for enrollment in the pivotal study of ISIS 420915 (CS2). Disease severity can also be assessed using the PND score, which is a 5-stage scoring system (Suhr et al. 1996). Life-threatening autonomic dysfunction develops in many patients, affecting the cardiocirculatory, gastrointestinal, and genitourinary systems. Symptoms include orthostatic hypotension, which can lead to dizziness, loss of consciousness and frequent falls. Gastrointestinal symptoms include diarrhea, severe constipation, alternating diarrhea/constipation, fecal incontinence, vomiting, and gastroparesis, all leading to progressive weight loss. Genito-urinary symptoms, including recurrent urinary tract infections, and, in men, erectile dysfunction may be present (Plante-Bordeneuve and Said 2011). Lifemexpectancy of patients with hATTR-PN is reported to be 5-12 years after diagnosis (Adams et al. 2012; Coelho et al. 2018). Patients typically die due to malnutrition and cachexia, renal failure, and cardiac disease (Coelho et al. 2008).

Cardiac involvement has been estimated to occur in 80% of TTR amyloidosis (Plante-Bordeneuve and Said 2011), manifested by restrictive cardiomyopathy and heart failure (Castano et al. 2015), conduction abnormalities and arrhythmias. Amyloid deposits in the kidney are common and can result in microalbuminuria with progression to renal failure in a subset of patients.

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

2.1.2. Overview of Target – Transthyretin

The name transthyretin (TTR) is derived from transporter of thyroxine and retinol and was formerly known as prealbumin. TTR is synthesized primarily in the liver and, to a lesser extent, by the choroid plexus and retina. A major function of TTR in the plasma is to transport retinol (vitamin A) to tissues and decrease urinary clearance of retinol through its association with retinol binding protein 4 (RBP4). About 70% of total body retinol is stored in the liver and mobilized into the blood stream bound to RBP4 (D'Ambrosio et al. 2011). The ratio RBP4:TTR in plasma is around 0.3 in healthy individuals, indicating that most of the circulating TTR remains free of RBP4 ligand (Buxbaum and Reixach 2009). Besides transporting the retinol-RBP4 complex, TTR also transports ~15% of plasma thyroxine with most of the thyroxine transported by either thyroxine binding globulin or albumin.

Recent evidence has suggested that TTR may also have a neuroprotective function in the brain. Brain TTR is produced primarily by the choroid plexus and has been proposed to help with nerve regeneration and to play a protective role in the Alzheimer's disease (Buxbaum and Reixach 2009; Fleming et al. 2009). It has been demonstrated that mice treated systemically with a TTR-specific antisense oligonucleotide (ASO) had decreased hepatic TTR mRNA levels and serum TTR concentration but did not show changes in the expression of TTR in the choroid plexus (Benson et al. 2006; Benson et al. 2017).

2.1.3. Current Therapies

Current therapeutic strategies to treat hATTR-PN include orthotopic liver transplant (OLT) or pharmacotherapy by stabilizing the TTR tetramers with Vyndaqel® (tafamidis) or off-label use of diflunisal, or by silencing the TTR protein production with Tegsedi™ (inotersen) or Onpattro™ (patisiran) (Coelho et al. 2012; Berk et al. 2013; Adams et al. 2016; Adams, Hawkins, et al. 2018; Benson et al. 2018).

Because most of the amyloidogenic-mutated TTR is secreted by the liver, OLT results in rapid disappearance of mutant TTR protein from the serum. However, wild-type TTR protein continues to be produced by the donor liver and can deposit in the pre-existing amyloid deposits in the tissues after transplantation, leading to continual disease progression and, in some cases, accelerating heart disease (Yazaki et al. 2000; Liepnieks and Benson 2007; Yazaki et al. 2007; Liepnieks et al. 2010). Younger patients with early disease, Val30Met (V30M) mutation, and mild symptoms (typically Stage 1) generally experience better outcomes with OLT. Stage 2

patients are often not candidates for OLT due to advanced age, cardiac involvement, or other health reasons (Herlenius et al. 2004; Stangou and Hawkins 2004).

Onpattro™ (patisiran) is a double-stranded small interfering RNA (siRNA) product which also works by inhibiting production of TTR protein; patisiran is approved in the United States and in the European Union for the treatment of the polyneuropathy of hATTR in adults. This drug is given intravenous (IV) every 3 weeks after patients are premedicated with high-dose dexamethasone. Tegsedi™ (inotersen) is an ASO drug administered once a week SC (Section 2.3.4); Tegsedi™ is authorized in the European Union, US and Canada for the treatment of Stage 1 or Stage 2 polyneuropathy in adult patients with hATTR-PN.

Vyndaqel® (tafamidis) which is a TTR stabilizer that works by preventing dissociation of the tetramer into amyloid-forming monomers, is indicated for the treatment of hATTR-PN in adult patients with Stage 1 polyneuropathy, and is currently approved for use in Europe, Japan, and several other countries. In some countries, tafamidis is also indicated for patients with more advanced stages of disease (Stage 2 and/or Stage 3). For patients with ATTR-CM in the United States, Vyndaqel®/Vyndamax™ (tafamidis) have been recently approved for ATTR-CM and have been shown to reduce all-cause mortality, and cardiac related hospitalizations due to ATTR.

Diflunisal is a non-steroidal anti-inflammatory drug (NSAID) that also acts as a TTR tetramer stabilizer and is not currently approved for the treatment of hATTR. Off-label use has been reported in patients with Stage 1 and Stage 2 disease (Adams et al. 2016); however, the known cardiovascular and renal side effects associated with the NSAID drug class may limit the use of this drug in older patients with hATTR-PN and concomitant cardiomyopathy and/or renal disease.

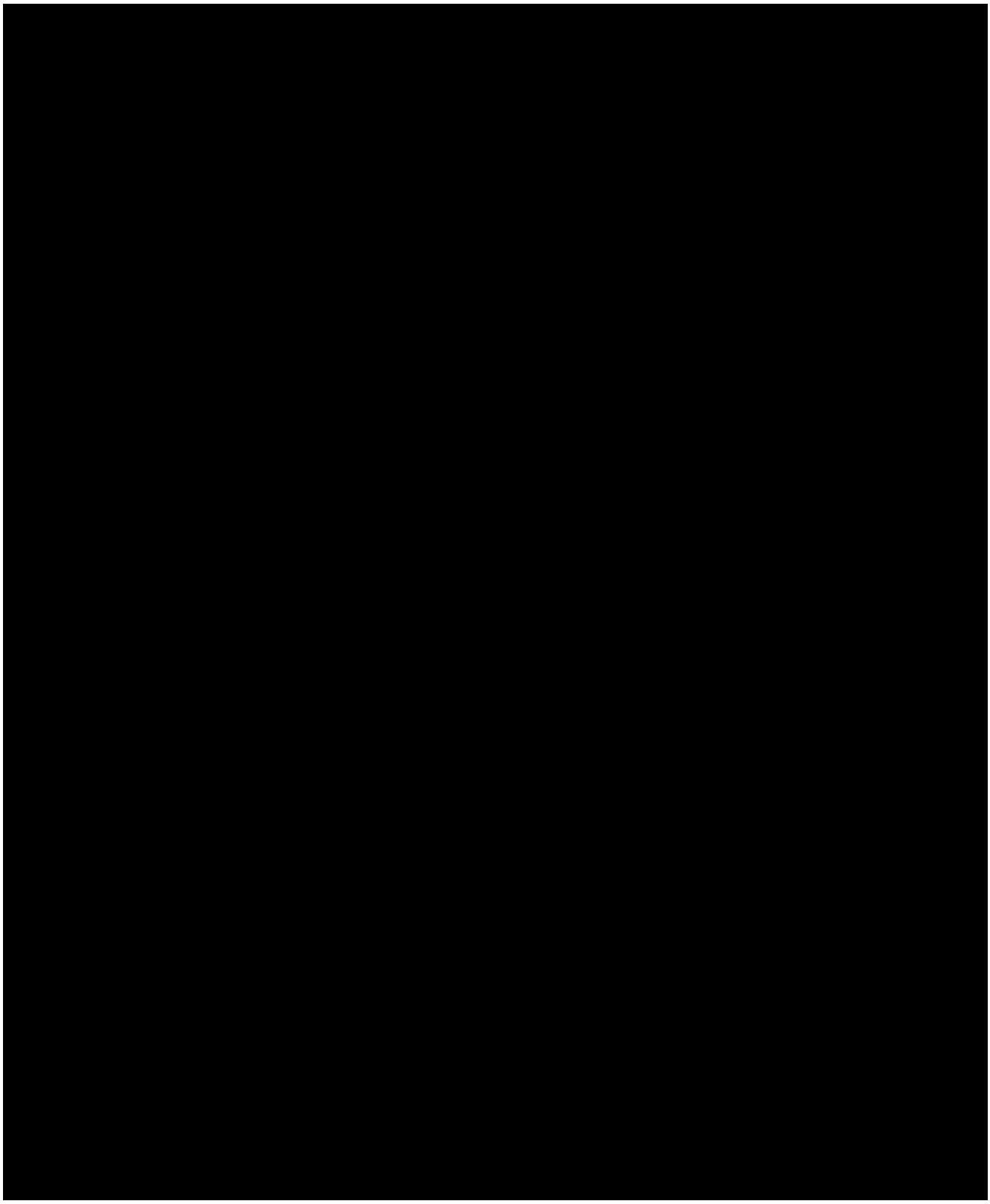
Consequently, there continues to be an unmet medical need for effective, well-tolerated and convenient treatments that do not require additional premedication for patients with hATTR-PN worldwide.

2.2. Therapeutic Rationale

[redacted] It should be noted that ASOs are highly charged hydrophilic molecules that do not cross the blood brain barrier (Levin et al. 2008) and thus systemic treatment with ION-682884 is not predicted to decrease levels of TTR in the brain.

It is predicted that decreasing the amount of liver-derived TTR protein circulating in the plasma by treatment with ION-682884 will result in a decrease in the formation of TTR amyloid fibril deposits, and thus slow, halt or even reverse disease progression. This strategy has been validated in the treatment of hATTR-PN patients through 2 recently approved drugs, i.e., inotersen (Benson et al. 2018) (an unconjugated 2′-MOE ASO that has the same base sequence as ION-682884) and patisiran (Adams, Gonzalez-Duarte, et al. 2018).

2.3. ION-682884



2.3.3. Preclinical Experience

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

The human TTR ASO, ISIS 420915 (inotersen), identified from a broad screen of ASOs targeted to various regions of the human TTR pre-mRNA, was demonstrated to be potent and efficacious in reducing human TTR mRNA expression in the human HCC cell line HepG2.

[redacted] ION-682884, was found to be significantly more potent that the unconjugated parent ASO, ISIS 420915, in inhibiting TTR mRNA expression in human hepatocytes *in vitro* (approximately 51-fold improvement in potency, IC_{50}), with the potential to greatly increase the safety margins.

The activity of ISIS 420915 has been characterized in both nonhuman primates and genetically modified mice. In human TTR transgenic mice, the ED_{50} values for human TTR hepatic mRNA and plasma protein reductions were 12.0 and 18.6 mg/kg/wk, respectively, following treatment with ISIS 420915 for 4 weeks. Treatment of cynomolgus monkeys with 50 mg/kg/wk ISIS 420915 for 12 weeks reduced TTR hepatic mRNA and plasma protein concentration by approximately 80%.

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

These results using human TTR transgenic mice strongly support GalNAc-conjugation to significantly increase ASO potency in inhibiting hepatic mRNA and plasma protein with lower doses providing the potential for improved safety.

2.3.4. Clinical Experience

Detailed information concerning the clinical studies conducted with ION-682884, as well as description of previous clinical experience with other related 2′-MOE phosphorothioate oligonucleotides, can be found in the Investigator's Brochure. A summary is included below.

ION 682884 has been evaluated in a Phase 1, double-blind, placebo-controlled clinical trial (ION-682884-CS1) in healthy volunteers to assess the tolerability, safety, PK, and PD of multiple and single doses of ION-682884. Four (4) cohorts of healthy volunteers were dosed at 45 mg once every 4 weeks for 4 months (Cohort A), 60 mg once every 4 weeks for 4 months (Cohort E), 90 mg once every 4 weeks for 4 months (Cohort B), and 120 mg as a single dose (Cohort C). Twelve (12) subjects were planned for each cohort, randomized 10:2 active drug to placebo, although for Cohort C only 11 subjects were enrolled (randomized 9:2). The mean percent change from Baseline in serum TTR in the multiple-dose cohorts at Day 99, 2 weeks after the fourth and last once-monthly dose, was -85.7 with 45 mg, -90.5 with 60 mg, and -93.8 with 90 mg. There were no serious adverse events (SAE), and no decrease in platelet count or renal function in the study. However, ALT increase was seen (< 3 × ULN) in some of the subjects in the 90 mg cohort. A clinical dosing regimen [redacted] administered once monthly

was selected for the Phase 3 studies of ION-682884, based on the Phase 1 safety and PD response data.

Inotersen (ISIS 420915) [redacted] has been evaluated in clinical studies in more than 270 patients, has shown an acceptable safety profile and has demonstrated clinical efficacy in terms of clinical pharmacodynamics (PD) as well as mNIS+7 and Norfolk QOL-DN assessments in hATTR-PN patients (Benson et al. 2018). Significant treatment effect with inotersen on serum TTR concentration was observed throughout the study in ISIS 420915-CS2 (Figure 2) with mean percent change from Baseline in circulating serum TTR concentration decreased steadily through Week 13 and sustained in steady state at 68.4% to 74.0% (median range: 74.6% to 79.0%) for the duration of the treatment (Yu et al. 2016a). In contrast, mean serum TTR concentration in the placebo group decreased by 8.5% at Week 3 and then remained fairly constant throughout the Treatment Period.

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

Changes from Baseline in Norfolk QOL-DN total score showed a statistically significant difference in favor of inotersen compared with placebo at both Week 35 and Week 66. The difference in LSMs between treatment groups was -6.14 (95% CI: -11.77, -0.52; p = 0.032) and -11.68 (95% CI: -18.29, -5.06; p < 0.0006) at Week 35 and Week 66, respectively (Figure 4).

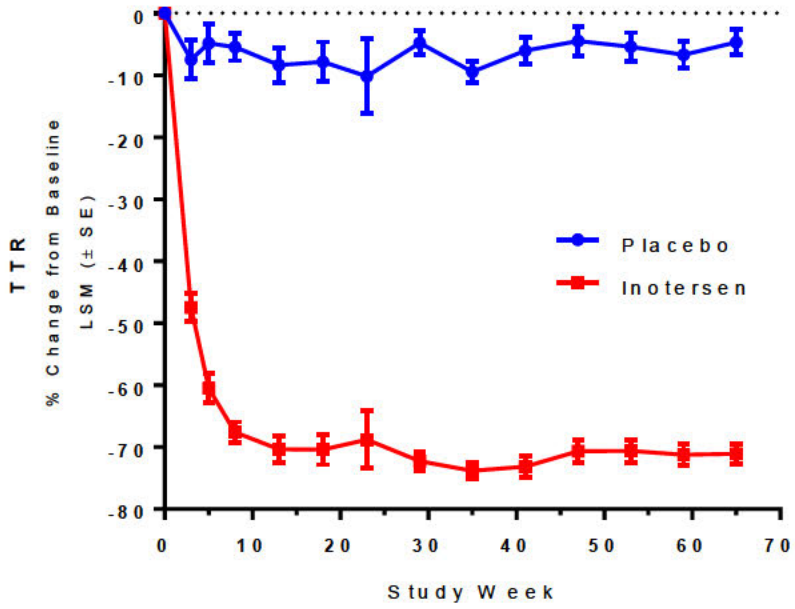


Figure 2: Percent Change from Baseline in TTR over Time (ISIS 420915-CS2 Full Analysis Set)

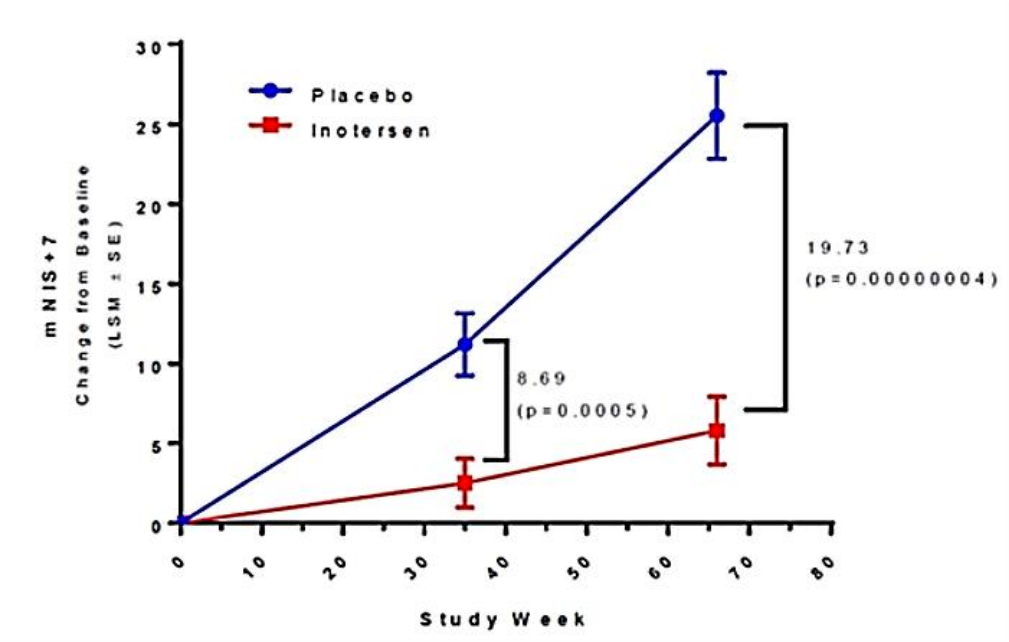


Figure 3: Change from Baseline in mNIS+7 over Time (ISIS 420915-CS2 Full Analysis Set)

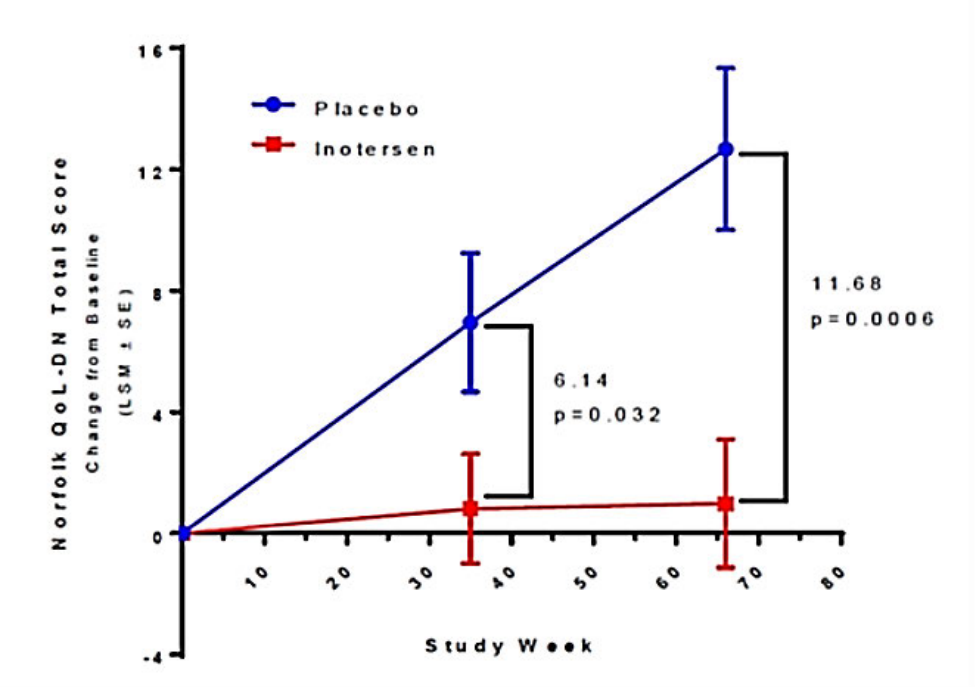
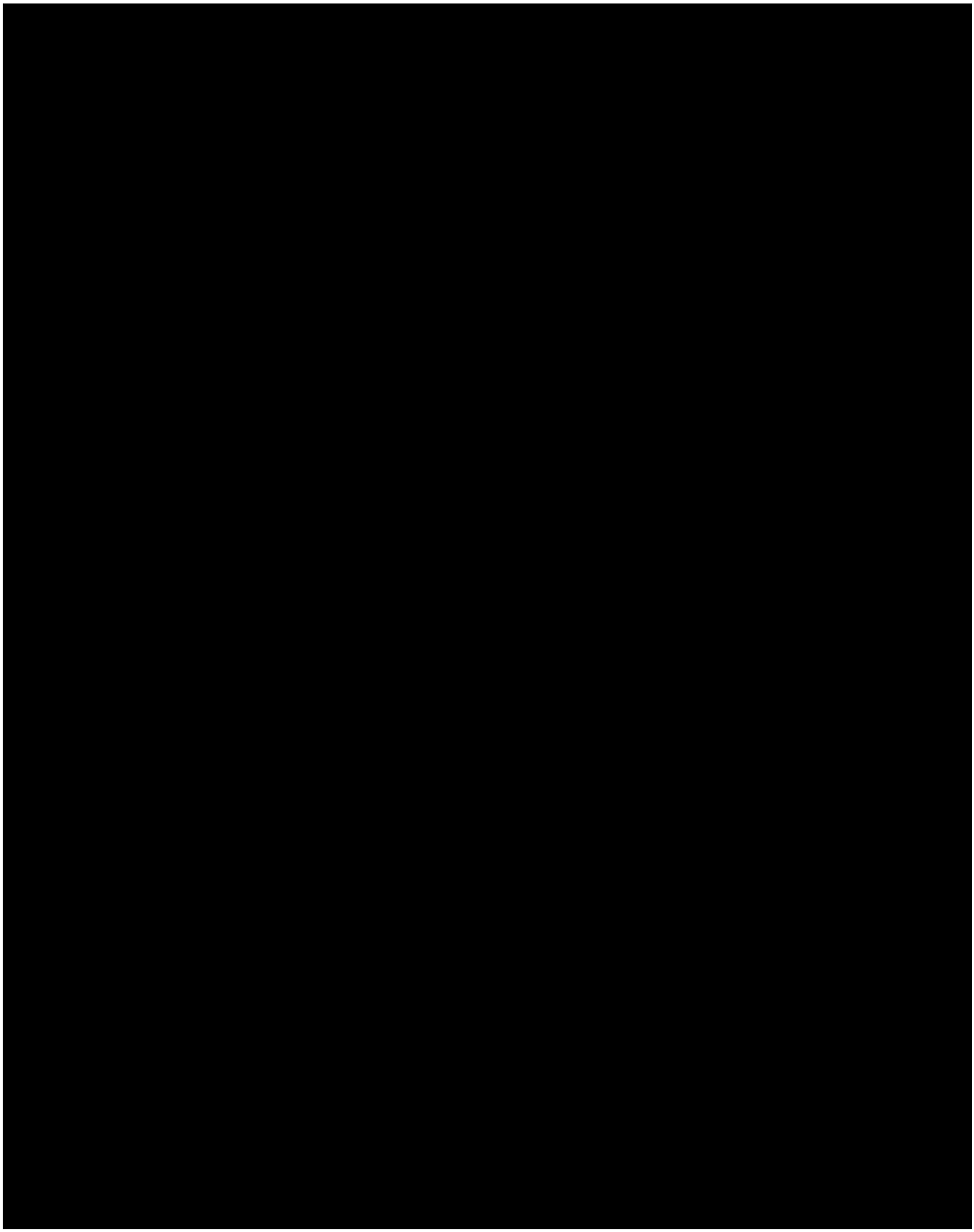


Figure 4: Change from Baseline in Norfolk-QOL-DN over Time (ISIS 420915-CS2 Full Analysis Set)



[redacted]

2.5. Benefit-Risk Assessment

2.5.1. Benefit Assessment

Administration of ION-682884 to patients may reduce the levels of mutated and wild-type TTR protein secreted by the liver, the primary source of TTR production and a primary organ for GalNAc-conjugated ASO distribution after systemic delivery. By decreasing the amount of liver-derived TTR protein circulating in the plasma, ION-682884 treatment should result in decreased formation of TTR amyloid fibril deposits and thus slow or halt disease progression, as measured by specific outcome measures, including mNIS+7, Norfolk-QOL-DN, R-ODS, NSC, SF-36, EQ-5D-5L, and COMPASS-31.

- mNIS+7 is a modified version of the Neuropathy Impairment Score (NIS) that has been used in two clinical trials in patients with hATTR-PN (Adams, Gonzalez-Duarte, et al. 2018; Benson et al. 2018). mNIS+7is a combination of a) NIS (motor, reflexes and sensory neurological evaluation), b) standardized quantitative sensory testing (heat pain and touch pressure at multiple body sites), c) composite nerve conduction score including five large fiber neurophysiological attributes, and d) autonomic function measured by the heart rate (HR) response to deep breathing.
- Norfolk QOL-DN is included to assess disease specific changes in the patients' perceived QOL. This instrument is a neuropathy-specific, 5-domain tool that has been validated in hATTR-PN patients (Vinik et al. 2014) and used in multiple pivotal trials for novel therapies for ATTR.
- Rasch-built overall disability scale (R-ODS) is a 24-item patient-reported outcome measure validated to measure activities of daily life in patients with inflammatory neuropathies (van Nes et al. 2011) and hATTR-PN (Adams, Gonzalez-Duarte, et al. 2018).
- Neuropathy Symptom Change (NSC) Score is a questionnaire composed of 38 questions that assess the presence and severity of these neuropathy symptoms (including weakness, loss of temperature and pain sensation, and manifestations associated with autonomic nervous system dysfunction).
- SF-36 is a non-disease specific tool to assess health related QOL; it is composed of 8 multi-item scales (35 items) assessing physical function (10 items), role limitations due to physical health problems (4 items), bodily pain (2 items), general health (5 items),

vitality (4 items), social functioning (2 items), role limitations due to emotional problems (3 items) and emotional well-being (5 items). These 8 scales can be aggregated into 2 summary measures: Physical (PCS) and Mental (MCS) Component Summary scores. The 36th item, which asks about health change, is not included in the scale or summary scores.

- EQ-5D-5L (The EuroQol Group) is a standardized quality of life assessment, used as a measure of health outcome, and composed of 5 questions in the following domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.
- COMPASS-31 (Sletten et al. 2012) is a questionnaire composed of 31 clinically selected questions evaluating 6 autonomic domains (orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor).
- PGIC is a global index that evaluates all aspects of patients' health and assesses if there has been an improvement or decline in clinical status; and PGIS is a global index that is used to rate the severity of a specific condition.

Many patients with hATTR-PN also have hATTR-CM. There is no widely-accepted method for measuring progression of cardiac disease in hATTR-CM. However, recent studies have shown that strain imaging with echocardiography or MRI can detect changes within a 1-year time frame (Falk 2011; Benson et al. 2017). In addition, the cardiac biomarker NT-proBNP has been shown to be elevated in patients with cardiac amyloidosis due to amyloid light amyloidosis (AL Amyloidosis) and to decline as cardiac function improves following removal of the amyloid forming light chain protein with chemotherapy (Palladini et al. 2006).

2.5.2. Risk Assessment

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

Thrombocytopenia and glomerulonephritis are potential considerations based on clinical findings with inotersen, the unconjugated form of ION-682884, [redacted] This dose is 27-fold higher exposure compared to the proposed dose of ION-682884 in the current study study. Frequent platelet, urine protein/creatinine ratio (UPCR), renal and hepatic function monitoring as well as stopping rules will be implemented in this study (see Sections 8.5 and 8.6). If the platelet result is unavailable (e.g., due to hemolysis, clumping, etc.) it must be repeated and reviewed prior to dosing during the Treatment Period.

Because TTR binds the retinol-RBP4 complex and prevents its excretion by the kidney, decreased plasma TTR concentration result in decreased circulating levels of both RBP4 and retinol. This has been shown with the naturally occurring TTR Ile84 mutation that disrupts the TTR-RBP4-retinol complex and results in low plasma levels of retinol (Waits et al. 1995). Prolonged reduction of circulating retinol could result in impaired delivery of retinol to peripheral tissues and consequent signs and symptoms of vitamin A deficiency such as night blindness, xerophthalmia or retinopathy. However, chylomicrons are believed to provide an alternative route of delivery of retinyl esters to peripheral tissues (Wei et al. 1995) and

chylomicron-delivered retinyl will not be affected by treatment with ION-682884. Indeed, preclinical studies utilizing TTR null mice have shown that although the mice have only 5–7% of circulating retinol and RBP4 levels compared to wild-type mice, they are viable and fertile, and do not show any observable symptoms of vitamin A deficiency (Episkopou et al. 1993; Wei et al. 1995). In addition, the levels of retinol within tissues such as the liver, kidney, testis and eye were similar in the TTR null mouse compared with wild-type controls (Wei et al. 1995). Furthermore, the retinal anatomy and function in these mice has been examined in detail with little effect found on the retinal structure or function (Bui et al. 2001). In addition, twins have been reported in the literature that have a genetic mutation in RBP4 that causes their RBP4 protein levels to be below the lower limit of quantification and also results in very low plasma retinol levels (Biesalski et al. 1999). In addition, mutations in the RBP4 gene have been identified in 2 teenage siblings with no detectable serum RBP and retinol levels less than 20% normal (Biesalski et al. 1999; Seeliger et al. 1999). Despite the low retinol, they have normal retinyl esters levels, normal absorption of fat and vitamin A after a meal challenge, and they have mild night blindness and a modest retinal dystrophy but no pronounced effects on growth or other physiologic functions that are normally affected during vitamin A deficiency. Taken together these findings imply that RBP4 is not essential for maintaining adequate tissue retinol levels. In addition, no imbalance of vitamin A deficiency was found in the NEURO-TTR trial after treatment with ISIS 420915, the unconjugated form of ION-682884, compared to placebo-treated patients. Nonetheless, to address the potential for impaired retinol delivery to tissues, in this study all patients will be required to take oral supplementation of the recommended daily allowance (RDA) of vitamin A (approximately 3000 IU vitamin A per day). In addition, an ocular questionnaires to screen for vitamin A deficiency will be performed periodically during the trial.

2.5.3. Overall Assessment of Benefit:Risk

Taking into account the measures taken to minimize risk to patients participating in this study, including frequent safety monitoring and supplementation with vitamin A, the potential risks identified in association with ION-682884 are justified by the anticipated benefits that may be afforded to patients with hATTR-PN.

3. EXPERIMENTAL PLAN

3.1. Study Design

This is a Phase 3 multicenter, open-label, randomized study of ION-682884 (eplontersen) in Stage 1 and Stage 2 hATTR-PN patients with a NIS of 10 to 130, with a concurrent reference arm of inotersen. Approximately 140 patients will be randomized 6:1 (ION-682884:inotersen) to receive [redacted] ION-682884 SC once every 4 weeks [redacted] or inotersen [redacted] SC once every week [redacted] Patients enrolled in the ION-682884 arm will be compared to patients enrolled in the placebo-cohort group in the ISIS 420915-CS2 (NEURO-TTR). An interim analysis will be conducted at Week 35 with primary efficacy analysis at Week 66. As both analyses will utilize comparisons to a control group external to the current study, the concurrent inotersen reference arm (n = 20) is intended to ensure that no gross differences in patient population and response exist between the NEURO-TTR and the current study. Patients in the

reference arm (inotersen) will be crossed over to ION-682884 once they complete Week 35 assessments. These patients will start ION-682884 at Week 37. All patients will continue dosing with ION-682884 until Week 81 with end-of-treatment (EOT) assessments at Week 85, 4 weeks after the last dose.

For patients randomized to ION-682884, attempts will be made to mirror NEURO-TTR distribution of patients according to disease stage (i.e., Stage 1-FAP vs. Stage 2-FAP).

Approximately 28 patients at selected sites (~22 on ION-682884 and ~6 on inotersen) will be enrolled in a PK subgroup and will receive additional sampling for PK as specified in the Schedule of Procedures (Appendix A).

Following treatment and the EOT assessments, eligible patients may elect to enroll in an OLE study pending study approval by the IRB/IEC and the appropriate regulatory authorities. All participating patients in the OLE study will continue to receive ION-682884 once every 4 weeks. Patients not participating in the OLE will enter the 20-week post-treatment evaluation portion of this study after completing the EOT assessments.

3.2. Number of Study Centers

This study will be conducted at multiple centers worldwide.

3.3. Number of Patients

Approximately 140 patients will be randomized 6:1 (ION-682884:inotersen) to receive [redacted] ION-682884 SC once every 4 weeks or inotersen [redacted] SC once weekly. For details about the rationale followed to determine the number of patients required see Section 10.2.

3.4. Overall Study Duration and Follow-up

This study will consist of the following periods:

- A ≤ 10-week Screening Period and Baseline/Day 1 Assessments
- A 84-week Treatment Period
- A 20-week Post-Treatment Evaluation Period/or enrollment into OLE study

Please refer to the Schedule of Procedures in Appendix A. Patients may be required to attend additional visits for monitoring of AE or abnormal investigation results. The frequency of additional monitoring will be determined after consultation between the Study Medical Monitor and the Investigator.

3.4.1. Screening and Baseline Assessment

Patient eligibility for the study will be determined within 10 weeks prior to study entry. The Baseline assessments should ideally be conducted after patient eligibility has been determined.

3.4.2. Treatment Period

The treatment and EOT Efficacy Assessment Period comprise approximately 84 weeks in total. Eligible patients will report to the Study Center for assessments at regular intervals throughout

the 80-week Treatment Period (Week 1 to Week 81). During the Treatment Period, ION-682884 is administered by SC injections every 4 weeks, and inotersen is administered by SC injection every week until Week 35. At Week 37, patients in the inotersen arm will be crossed-over to ION-682884. After the Treatment Period is complete, patients will report to the Study Center during Week 85 for the EOT efficacy assessments.

3.4.3. Post-Treatment Evaluation Period and Long-Term Follow up

Patients must complete follow-up visits on Weeks 89, 93, 97, 101 and 105; the visits on Weeks 93 and 105 are mandatory in-clinic visits. The final study visit will be on Week 105. Alternatively, after completion of the EOT Efficacy Assessment Period, eligible patients (including patients that initially received inotersen) may elect to enroll in an OLE study where they will receive ION-682884 once every 4 weeks, pending study approval by the IRB/IEC and appropriate regulatory authority. In this case, patients will not participate in the Post-Treatment Evaluation Period.

3.5. End-of-Study

The Primary Completion Date, defined as "the date on which the last participant in a clinical study was examined or received an intervention/treatment to collect final data for the primary outcome measures" is the last patient Week 66 study visit.

The Study Completion Date is the last patient last visit (Week 105) at the end of the Post-treatment Evaluation Period.

3.6. Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will be assembled and meet periodically to review safety, tolerability and efficacy data collected on ION-682884 and inotersen, and to review the results of the predetermined interim analysis at Week 35. Based on its assessment of the safety, tolerability and efficacy of ION-682884 and inotersen, the DSMB will provide recommendations to the Sponsor for modifying, stopping, or continuing the study as planned. Details on the safety assessments, frequency of review, meeting schedules and controlled access to data are outlined in the DSMB Charter and Statistical Analysis Plan (SAP).

4. PATIENT ENROLLMENT

4.1. Screening

Before patients may be enrolled into the study, the Sponsor or designee requires a copy of the Study Center's written IEC/IRB approval of the protocol, informed consent form, and all other patient facing information and/or recruitment material.

Patients or their legally acceptable representatives 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 and will be assigned a unique screening number before any study procedures, including Screening procedures, are performed. At the time of randomization, patients will be assigned a unique patient identification number. This number will be used to

identify the subject throughout the trial and must be used on all study documentation related to that subject. The screening number and patient identification number must remain constant throughout the entire trial. In the event the subject is re-consented and re-screened the subject must be given a new screening number. Screening numbers and patient identification numbers, once assigned, will not be re-used.

4.2. Randomization

Patients will be randomized after all Screening assessments have been completed and after the Investigator has verified that they are eligible per criteria in Section 5.1 Section 5.2. No patient may begin treatment prior to randomization and assignment of a unique patient identification number.

Using an Interactive Voice/Web-Response System (IXRS), eligible patients will be randomized 6:1 to receive ION-682884 or inotersen, respectively. Attempts will be made to mirror the NEURO-TTR distribution of patients according to disease stage (i.e., Stage 1-FAP vs. Stage 2-FAP).

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 10 weeks of Study Day 1, or at the time point specified in the individual eligibility criterion listed. The Sponsor Medical Monitor may be consulted if any questions arise regarding the inclusion or exclusion criteria.

5.1. Inclusion Criteria

1. Must have given written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements
2. Aged 18 to 82 years at the time of informed consent
3. Satisfy the following:
    a. Females: must be non-pregnant and non-lactating and either;
        i. surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy)
        ii. Post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved)
        iii. Abstinent* or

iv. If engaged in sexual relations of child-bearing potential, agree to use highly effective contraceptive methods (refer to Section 6.3.1) from the time of signing the informed consent form until at least 24 weeks after the last dose of ION-682884 or inotersen and agree to receive a once every 4 weeks pregnancy test

b. Males: Surgically sterile (i.e., bilateral orchidectomy) or if engaged in sexual relations with a woman of child-bearing potential (WOCBP), the patient or the patient's non-pregnant female partner must use a highly effective contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 24 weeks after the last dose of ION-682884 or inotersen.

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

4. hATTR-PN as defined by meeting all 3 of the following criteria:
   a. Stage 1 (ambulatory without assistance) or Stage 2 (ambulatory with assistance) according to the Familial Amyloid Polyneuropathy (FAP) or Coutinho Stage
   b. Documented genetic mutation in the TTR gene
   c. Symptoms and signs consistent with neuropathy associated with transthyretin amyloidosis, including NIS ≥ 10 and ≤ 130
5. Willingness to adhere to vitamin A supplementation per protocol

5.2. Exclusion Criteria

1. Clinically significant abnormalities in medical history (e.g., previous acute coronary syndrome within 6 months of Screening, major surgery within 3 months of Screening) or physical examination
2. Screening laboratory results as follows, or any other clinically significant abnormalities in screening laboratory values that would render a patient unsuitable for inclusion:
   a. Urine protein/creatinine ratio (UPCR) ≥ 1000 mg/g. In the event of UPCR above this threshold, eligibility may be confirmed by a repeat random urine test with UPCR < 1000 mg/g or a quantitative total urine protein measurement of < 1000 mg/24 hr
   b. Renal insufficiency as defined by estimated glomerular filtration rate ($eGFR_{creat-cys}$) < 45 mL/min/1.73 m^2 at Screening ($eGFR_{creat-cys}$ is calculated using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] creatinine-cystatin C equation from 2012) (Inker et al. 2012)
   c. Positive test for blood (including trace) on urinalysis that is subsequently confirmed with urine microscopy showing > 5 red blood cells per high power field and is related to glomerulopathies. In women, this exclusion criterion must be assessed outside of menstrual period. If in the opinion of the Investigator the hematuria is not considered

related to glomerulopathies the patient may be considered eligible, pending proper follow-up and a discussion with the medical monitor. Patients with history of bladder cancer must have been treated with curative intent and have not presented recurrence within the prior 5 years.

d. Alanine aminotransferase/ aspartate aminotransferase (ALT/AST) > 2 × upper limit of normal (ULN)

e. Bilirubin ≥ 1.5 × ULN (patients with bilirubin ≥ 1.5 × ULN may be allowed on study if indirect bilirubin only is elevated, ALT/AST is not greater than the ULN and known to have Gilbert's disease)

f. Platelets < 125×10^9/L

g. HbA1C ≥ 7%

h. Abnormal thyroid function tests with clinical significance per Investigator judgement

3. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1
4. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator
5. Known history of or positive test for human immunodeficiency virus (as evidenced by positive tests for HIV antibody and HIV RNA), hepatitis C (as evidenced by positive tests for HCV antibody and HCV RNA) or hepatitis B (as evidenced by a positive test for hepatitis B surface antigen)
6. Uncontrolled hypertension (BP > 160/100 mm Hg)
7. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin, melanoma *in situ*, prostate carcinoma grade group 1, breast ductal carcinoma *in situ*, or carcinoma *in situ* of the cervix. Patients with a history of other malignancies who have been treated with curative intent and without recurrence within 5 years may also be eligible per Investigator judgement.
8. Current treatment with any approved drug for hereditary TTR amyloidosis such as Vyndaqel® / Vyndamax™ (tafamidis), Tegsedi™ (inotersen), Onpattro™ (patisiran), off-label use of diflunisal or doxycycline, and tauroursodeoxycholic acid (TUDCA). If previously treated with Vyndaqel® / Vyndamax™, diflunisal or doxycycline, and TUDCA, must have discontinued treatment for 2 weeks prior to Study Day 1
9. Current of previous treatment with Tegsedi™ (inotersen) or Onpattro™ (patisiran) or other oligonucleotide or RNA therapeutic (including siRNA). This exclusion criterion does not apply to COVID-19 mRNA vaccinations.
10. Treatment with another investigational drug, biological agent, or device within 3 months of screening, or 5 half-lives of study agent, whichever is longer
11. History of bleeding, diathesis or coagulopathy (e.g., liver cirrhosis, hematologic malignancy, antiphospholipid antibody syndrome, congenital disorders such as hemophilia A, B, and Von Willebrand disease)

12. Recent history of, or current drug or alcohol abuse.
13. Use of oral anticoagulants, unless the dose has been stable for 4 weeks prior to the first dose of ION-682884 or inotersen and regular clinical monitoring is performed
14. Karnofsky performance status ≤ 50%
15. Other causes of sensorimotor or autonomic neuropathy (e.g., autoimmune disease, diabetic neuropathy)
16. Prior liver transplant or anticipated liver transplant within 1 year of Screening
17. New York Heart Association (NYHA) functional classification of ≥ 3
18. Known immunoglobulin light chain amyloidosis (AL amyloidosis)
19. Known leptomeningeal amyloidosis
20. Known multiple myeloma
21. Monoclonal gammopathy of undetermined significance (MGUS) and/or alterations in immunoglobulin free light chain (FLC) ratio, unless fat, bone marrow, or heart biopsy confirming the absence of light chain and the presence of TTR protein by mass spectrometry or immunoelectron microscopy. For patients with CKD and without presence of monoclonal protein in blood and urine, the acceptable FLC ratio is 0.26-2.25. Results different from that may be discussed with local hematologist, Investigator and Medical Monitor if the risks associated with the biopsy outweigh the benefits.
22. Presence of known type 1 or type 2 diabetes mellitus
23. Anticipated survival less than 2 years
24. Have any other conditions, which, in the opinion of the Investigator would make the patient unsuitable for inclusion, or could interfere with the subject participating in or completing the study

6. STUDY PROCEDURES

6.1. Study Schedule

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

6.1.1. Screening and Baseline Assessments

Before any study-specific procedures or evaluations are initiated, patients must sign and date the informed consent form. If required, the informed consent may be administered remotely using locally accepted methods. An up to 10-week period is given to perform the screening evaluations and Baselines assessments. An abnormal screening result may be retested if Investigator believes and documents that the results are artifactual. An NIS assessment is performed at screening to determine patient eligibility only. This assessment does not include the +7 components. TTR genotyping is only conducted if previous results are not already available.

Baseline assessments can be conducted during the 10-week screening window and should ideally be performed after patient eligibility has been determined. Appendix A details which Baseline assessments should be completed before Study Day 1.

Laboratory collections can be performed by a home health-care provider instead of in-clinic. Biopsy for verification of amyloid deposition is not required as part of the eligibility but can be performed per Investigator judgment.

The study site will record patient's basic personal details, including name, contact details, gender, date of birth, age, and self-reported ethnicity and racial origin (to be used only for clinical purposes), as well as information on each patient's medical history, and clinical data collected about his/her participation in the study.

The 2 mNIS+7 assessments must be performed within 21 days prior to the first dose of ION-682884 or inotersen (Day 1) and the second mNIS+7 assessment must be conducted ≥ 1 day apart from the first assessment. In addition, every effort should be made to conduct the 2 assessments < 7 days apart. If a blood draw is to be performed on a mNIS+7 assessment day, they must be performed after the mNIS+7 assessment is complete. The mNIS+7 assessment procedure includes the NIS, sensory and motor nerve conduction testing, quantitative sensory testing and measurement of heart-rate variation with breathing. The NSC score is collected during the NIS assessment procedure but is analyzed separately.

6.1.2. Day 1/Randomization

During the Day 1 study visit, patients will report to the Study Center for evaluations, randomization, and ION-682884 or inotersen administration (first dosing should be the last procedure of Day 1 study visit). See Appendix A for the assessments that should be performed on Day 1.

For a visit where Norfolk QOL-DN is to be administered, it must be the first assessment performed at the visit. Baseline Norfolk QOL-DN can be administered on the same day as the first mNIS+7 assessment, but must be performed prior to the mNIS+7 assessment.

For an individual patient, every effort should be made to ensure the same mNIS+7 evaluator performs all of the mNIS+7 assessments throughout the study. In addition, the mNIS+7 evaluator must be insulated from the patient's general study procedures and knowledge of the patient's AEs.

6.1.3. Treatment Period

During Study Week 1, patients will report to the Study Center for evaluations and ION-682884 or inotersen administration on Day 1. After Week 1, ION-682884 will be administered once every 4 weeks through the end of the Treatment Period. Inotersen will be administered once weekly up to and including Week 34 at which time patients will transition to every 4 week administration of ION-682884.

For patients randomized to the ION-682884 treatment arm, there will be a total of 43 visits during Weeks 1- 83 for ION-682884 administration and other study procedures (see Schedule of Procedures in Appendix A). Eleven of the 43 visits are mandatory in-clinic visits, whereas

32 visits can be completed either in-clinic, at home by a home health-care provider (if approved locally), or by using a local laboratory upon Investigator approval.

For patients randomized to the inotersen reference arm, there will be a total of 60 visits during Weeks 1-83 for Study Drug administration and other study procedures (see Schedule of Procedures in Appendix A). Eleven of the 60 visits are mandatory in-clinic visits, whereas 49 visits can be completed either in-clinic, at home by a home health-care provider (if approved locally), or by using a local laboratory upon Investigator approval.

During an clinic visit, all blood samples should be drawn prior to ION-682884 or inotersen administration (exceptions are the post-dose samples in the PK subgroup). ION-682884 or inotersen may be administered by either Study Center personnel (during a clinic visit) or at home by the patient/caregiver/home health-care provider (See Section 8.1). Dosing instructions and training will be provided to the patient on Day 1 and to any caregiver, as needed.

For patients in the inotersen treatment arm, the last inotersen dose will be at Week 34. On Weeks 35 and 36 there is no dosing with inotersen. Patients in the inotersen treatment arm will complete the Week 35 assessments and then cross over to ION-682884 once-every-4-weeks treatment starting at Week 37.

In addition to ION-682884 or inotersen, patients will also take daily supplemental doses of the RDA of vitamin A (approximately 3000 IU vitamin A or similar dose as available in the region in which the patient resides). Vitamin A may be taken 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 Period. Vitamin A supplement at doses more than the RDA is not recommended.

Vitamin A deficiency will be monitored by having the patient periodically complete a vitamin A deficiency screening questionnaire (called “ocular questionnaire”). In cases of suspected vitamin A deficiency, a consultation with ophthalmologist may be requested by the Investigator, if deemed necessary, after discussing with the Medical Monitor.

For Weeks 35, 37, 65 and 66 there is a ± 10 days window; for all other visits, there is a ± 7 days window. All reasonable attempts should be made to ensure compliance with the visit schedule as outlined in the Schedule of Procedures (Appendix A). However, in the event that a visit does not occur or is delayed, all subsequent visits should be calculated based on the time elapsed since Day 1 rather than from the date of the previous visit.

Patients randomized to the ION-682884 treatment arm will have their platelet count, eGFR, UPCR, and LFTs assessed once every 4 weeks during the Treatment Period.

Patients randomized to the inotersen reference arm will have their platelet count, eGFR, UPCR, and LFTs assessed every 2 weeks during the Treatment Period up to and including Week 34. After Week 34, patients assigned to the inotersen reference arm will transition to receive ION 682884 through the end of the Treatment Period. After patients in the inotersen reference arm transition to ION-682884, they will continue to have every 2-week platelet count, eGFR, UPCR, and LFTs measurements for 8 weeks after their last dose of inotersen. They will then be assessed every 4 weeks for platelet count, eGFR, UPCR, and LFTs through the end of the Treatment Period.

The window for blood collections that occur outside clinic visits is ± 4 days. See Section 8.5 for guidance on ION-682884 or inotersen dosing relative to hematology and chemistry monitoring.

Key efficacy endpoints (serum TTR reduction, mNIS+7, Norfolk QOL-DN) will be assessed at 3 landmark visits (Weeks 35, 66, and 85). Patients will be encouraged to complete these visits even if on dose pause or if treatment has been permanently discontinued prematurely.

6.1.4. End-of-Treatment Assessment Visit

The EOT efficacy assessments are conducted at Week 85 and should be performed within 28 days from the last dose of ION-682884. For those who do not complete dosing, please see Section 8.8 for guidance on follow-up procedures.

6.1.5. Post-Treatment Evaluation Period

After completion of the EOT efficacy assessment, patients will complete the Post-Treatment Evaluation Period which consists of 5 study visits on Weeks 89, 93, 97, 101 and 105, as outlined in the schedule of procedures (Appendix A). Alternatively, after completion of the EOT efficacy assessment, eligible patients may elect to receive ION-682884 in an OLE study, pending study approval by the IRB/IEC and the appropriate regulatory authority. In this case, patients will not participate in the Post-Treatment Evaluation Period.

6.2. Laboratory Assessments

Laboratory analyte samples will be collected throughout the study. A list of these analytes is contained in Appendix B. All patients will be required to fast for 8–10 hours before assessment of retinyl palmitate (Weeks 1, 13, 25, 37, 49, 65, 85, 93, and 105). Collection of laboratory samples for assessment of serum vitamin A levels should precede the ingestion of vitamin A or multivitamin supplement for that day (Screening/Baseline, Weeks 1, 13, 25, 37, 49, 65, 85, 93, and 105). During this time, the patient can drink water and they should ensure that they do not become dehydrated.

If the results of these assessments are uninterpretable (e.g., missing sample, hemolysis) the Investigator should request a new test as soon as possible. If evaluable results for platelets, eGFR or UPCR are not available for the Investigator to review by the date of administration of the Study Drug, or the results are from an assessment older than 14 days ±7 days from the dosing day (±7 days allows for visit window), the patient should be instructed to hold dosing until the new results are available and interpretable. Note: if there are 2 sets of lab value results within the previous 14 days ±7 days of the dosing day, the most recent one should be used for deciding whether dose administration should proceed. Please see Section 8.5 for more detail.

6.3. Restriction on the Lifestyle of Patients

6.3.1. Contraception Requirements

All male patients and WOCBP must refrain from sperm/egg donation and either be abstinent[†] or use highly effective contraception from the time of signing the informed consent form until at least 24 weeks after their last dose of study treatment.

For male patients engaged in sexual relations with a WOCBP, the patient or the patient's non-pregnant female partner must use a highly effective contraception method from the time of signing the informed consent form until at least 24 weeks after their last dose of ION-682884 or inotersen. Male patients with partners that are pregnant must use condoms to ensure that the fetus is not exposed to the ION-682884 or inotersen.

For the purposes of this study, WOCBP are defined as any female who has experienced menarche, and who does not meet 1 of the following conditions:

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

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

For male patients:

- Highly effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the non-pregnant female partner of WOCBP uses a highly effective contraceptive method (defined below)
- Male patients with partners that are pregnant must use condoms as contraception to ensure that the fetus is not exposed to the ION-682884 or inotersen

For female patients and female partners of male patients, highly effective female contraception methods comprise:

- Surgical sterilization (e.g., bilateral tubal occlusion), hormonal contraception associated with inhibition of ovulation (combined estrogen and progestogen containing), intrauterine contraception device or intrauterine hormone-releasing system (IUS)

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

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

6.3.2. Other Requirements

All patients will be required to fast for 8–10 hours before assessment of retinyl palmitate (Weeks 1, 13, 25, 37, 49, 65, 85, 89, 93, and 105. Collection of laboratory samples for assessment of serum vitamin A levels should precede the ingestion of vitamin A or multivitamin supplement for that day (Screening/Baseline, Weeks 1, 13, 25, 37, 49, 65, 85, 89, 93, and 105).

All other blood tests performed on those weeks can be done on samples collected while non-fasting.

7. ION-682884 / ISIS 420915 (INOTERSEN)

ION-682884 and inotersen characteristics are listed in Table 1.

7.1. ION-682884 / ISIS 420915 Description

7.1.1. ION-682884 (Eplontersen)

ION-682884 [redacted] storage and preparation instructions will be provided by the Sponsor. ION-682884 must be stored securely [redacted] and be protected from light.

7.1.2. ISIS 420915 (Inotersen)

ISIS 420915, [redacted] storage and preparation instructions will be provided by the Sponsor. ISIS 420915 must be stored securely [redacted] and be protected from light.

Table 1: ION-682884 / ISIS 420915 (Inotersen) Characteristics

ION-682884 / Inotersen	ION-682884	ISIS 420915 (Inotersen)
Strength	[redacted]	[redacted]
Volume/Formulation	[redacted]	[redacted]
Administration	SC once every 4 weeks	SC once every week

7.2. Packaging and Labeling

The Sponsor will provide the Investigator with packaged ION-682884 and inotersen labeled in accordance with specific country regulatory requirements.

7.3. ION-682884 / ISIS 420915 (Inotersen) Accountability

The study staff is required to document the receipt, dispensing, and return/destruction of ION-682884 or ISIS 420915 supplies provided by the Sponsor according to Sponsor instructions and in accordance with institutional policy.

8. TREATMENT OF PATIENTS

8.1. ION-682884 / ISIS 420915 (Inotersen) Administration

ION-682884 and inotersen will be provided for single use only. ION-682884 and inotersen will be administered by SC injection.

ION-682884 or inotersen can be administered in the clinic during clinic visits per protocol or administered at home by the patient/caregiver/home health-care provider after clinic visits. For weeks that do not include a clinic visit, ION-682884 or inotersen may be administered by either Study Center personnel (in which case additional clinic visits will occur) or at home by the patient/caregiver/home health-care provider. Dosing instructions and training will be provided to the patient on Day 1 and as needed.

Weekly inotersen administration has a window of ± 4 days. Once-every-4-weeks ION-682884 administration has a window of ± 7 days.

Please refer to the ION-682884 and inotersen manuals provided by the Sponsor for more detailed instructions for ION-682884 and inotersen preparation and administration.

Table 2: ION-682884 / ISIS 420915 (Inotersen) Dosing Information

Study Drug	Volume to Administer	Total Dose
ION-682884	[redacted]	[redacted]
ISIS 420915 (Inotersen)	[redacted]	[redacted]

8.2. Other Protocol-Required Drugs

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

8.3. Other Protocol-Required Treatment Procedures

There are no other protocol-required treatment procedures.

8.4. Treatment Precautions

There are no specific treatment precautions required for this study.

8.5. Safety Monitoring Rules

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

For the purposes of safety monitoring for liver chemistry tests, renal parameters, and platelet count, "Baseline" is defined as:

- The average of the pre-dose test closest to Day 1 and Day 1. The window for blood collections (hematology and chemistry) that occur outside clinic visits is ± 4 days

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

Confirmation Guidance: At any time during the study (Treatment or Post-Treatment Periods), the initial clinical laboratory results meeting the safety monitoring criteria presented below **must be confirmed** by performing measurements (ideally in the same laboratory that performed the initial measurement) on new specimens. All new specimen collections should take place as soon as possible (ideally within 3 days of the initial collection). For stopping rules, if the initial laboratory result is observed during the Treatment Period, the results from the retest **must be available** prior to administering the next dose of ION-682884 or inotersen.

Re-dosing Guidance: Patients with initial laboratory test values that reach a stopping rule must not be re-dosed until the re-test results are available. In general, patients who do not meet the stopping rules based upon retest may continue dosing. However, the Investigator and the Sponsor Medical Monitor (or appropriately qualified designee) should confer as to whether additional close monitoring of the patient is appropriate. If any of the stopping criteria described below (refer to Section 8.6.1 through Section 8.6.3) are met, the patient will be permanently discontinued from further treatment with ION-682884 or inotersen, evaluated fully as outlined below and in consultation with the Sponsor Medical Monitor or appropriately qualified designee, and will be followed up in accordance with Section 8.8 of the protocol.

8.5.1. Safety Monitoring Rules for Liver Chemistry Tests

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

Monitoring frequency will be once every 4 weeks in patients randomized to the ION-682884 treatment arm until the end of the Treatment Period.

Patients randomized to the inotersen reference arm will have their liver chemistry assessed every 2 weeks during the Treatment Period up to and including Week 34. After patients in the inotersen reference arm transition to ION-682884 they will continue to have every 2 week liver chemistry measurements for 8 weeks after their last dose of inotersen. They will then be assessed every 4 weeks, through the end of the Treatment Period.

For inotersen patients who terminate treatment before the end of the Treatment Period, liver chemistry measurements should be monitored once every 2 weeks, for a duration of 8 weeks.

In the event of an ALT or AST measurement that is > 3 × ULN (or 2 × Baseline value if the Baseline value was > ULN) at any time during the study (Treatment or Post-Treatment Period), repeat testing should be performed within 48 to 72 hours of liver chemistry tests (ALT, AST, ALP, total bilirubin and international normalized ratio [INR]) to confirm the abnormalities and to determine if they are increasing or decreasing. There also should be inquiry made about symptoms. Additional, confirmatory measurements should also be performed if ALT or AST levels increase to 5 × ULN.

If new onset symptoms of anorexia, nausea, fatigue, right upper abdominal discomfort, vomiting present with unclear etiology, liver enzymes should be measured.

Frequency of Repeat Measurements: Patients with confirmed ALT or AST levels > 3 × ULN (or 2 × Baseline value if the Baseline value was > ULN) should have their liver chemistry tests

(ALT, AST, ALP, INR and total bilirubin, direct and indirect bilirubin) retested 2 or 3 times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic (see below).

Further Investigation into Liver Chemistry Elevations: For patients with confirmed ALT or AST levels > 3 × ULN (or 2 × Baseline value if the Baseline value was > ULN), the following evaluations should be included in the work up:

- Obtain a more detailed history of symptoms and prior and concurrent diseases
- Obtain further history for concomitant drug use (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
- Obtain a history for exposure to environmental chemical agents and travel
- Serology for viral hepatitis (HAV immunoglobulin M [IgM], HBsAg, HCV antibody, cytomegalovirus [CMV] IgM, and EBV antibody panel)
- Serology for autoimmune hepatitis (e.g., antinuclear antibody [ANA], antismooth muscle antibody, type 1 anti-liver kidney microsomal antibody)

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

8.5.2. Safety Monitoring for Renal Function

Serum creatinine, estimated glomerular filtration rate ($eGFR_{creat-cys}$, calculated using the CKD-EPI creatinine-cystatin C equation [2012]), urinalysis, and UPCR should be monitored every 4 weeks in all patients randomized to the ION-682884 treatment arm and every 2 weeks in all patients randomized to the inotersen reference arm, up to and including Week 34. After Week 34, patients assigned to the inotersen reference arm will transition to receive ION-682884 through the end of the Treatment Period. After patients in the inotersen reference arm transition to ION-682884, they will continue to have every 2-week measurements for 8 weeks after their last dose of inotersen. They will then be assessed every 4 weeks through the end of the Treatment Period..

For inotersen patients who terminate treatment before the end of the Treatment Period, renal function should be monitored once every 2 weeks, for a duration of 8 weeks..

In the event of a confirmed (as described in Section 8.5) laboratory result meeting 1 or more of the following criteria:

a. Creatinine clearance ($eGFR_{creat-cyst}$) decrease from Baseline > 25%
b. UPCR > 3 × Baseline AND > 1000 mg/g

Renal function will be monitored weekly until further work up and/or resolution per Investigator judgment in consultation with the Medical Monitor. If there is further worsening in renal function, refer to Section 8.6.2 for guidance.

8.5.3. Safety Monitoring Rules for Platelet Count Results

Please refer also to Table 3 and Table 4.

Platelet count monitoring frequency will be once every 4 weeks in patients randomized to the ION-682884 treatment arm until the end of the Treatment Period.

Patients randomized to the inotersen reference arm will have their platelet count assessed every 2 weeks during the Treatment Period up to and including Week 34. After Week 34, patients assigned to the inotersen reference arm will transition to receive ION-682884 through the end of the Treatment Period. After patients in the inotersen reference arm transition to ION-682884, they will continue to have every 2-week platelet count measurements for 8 weeks after their last dose of inotersen. They will then be assessed every 4 weeks for platelet count through the end of the Treatment Period.

For inotersen patients who terminate treatment before the end of the Treatment Period, platelets should be monitored once every 2 weeks, for a duration of 8 weeks.

The Investigator should document review of all platelet count results within 48 hours of receipt.

For patients on ION-682884 or inotersen, if a patient's platelet count falls to less than 100×10^9/L but more than 75×10^9/L, then the patient's platelet counts should be monitored weekly. In case of platelet reduction to below 75×10^9/L, the platelet monitoring rules for ION-682884 or inotersen defined in Stopping rules (Section 8.6.3, Table 4) should be followed. If a patient's platelet count falls to $\leq 50 \times 10^9$/L, the Investigator must communicate to the Sponsor within 24 hours of receiving the platelet result.

Treatment should be withheld if there is no evaluable platelet count within 14 days ±7 days prior to the scheduled dose. Any unreportable platelet count result must be rechecked and determined not to have met a stopping rule before dosing can continue.

In the event of a platelet count $< 100 \times 10^9$/L, additional laboratory investigations may be conducted (Table 3).

Table 3: Additional Labs to be Performed in the Event of a Platelet Count < 100 × 10^9/L

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

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

8.5.4. Safety Monitoring for Minor Bleeding Events

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

8.5.5. Safety Monitoring Rules for Ocular Effects

An ocular questionnaire designed to screen for vitamin A deficiency will be administered periodically (every 2 to 3 months) during Treatment Period. Any patient who presents with new and 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 additional work up with a corneal specialist should be considered. 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.

Dosing with ION-682884 or inotersen may continue while these evaluations are being performed.

8.6. Stopping Rules

For the purposes of the stopping rules, Baseline is defined as: average of the pre-dose test closest to Day 1 and Day 1.

8.6.1. Stopping Rules for Liver Chemistry Elevations

In the event of laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor,** dosing of a patient with ION-682884 or inotersen will be stopped permanently; values that are not confirmed due failure to retest or missing lab values will be presumed confirmed:

1. ALT or AST > 8 × ULN, which is confirmed
2. ALT or AST > 5 × ULN, which is confirmed and persists for ≥ 2 weeks
3. ALT or AST > 3 × ULN (or 2 × Baseline value if the Baseline value was > ULN), which is confirmed **and** total bilirubin > 2 × ULN or INR > 1.5
4. ALT or AST > 3 × ULN (or 2 × Baseline value if the Baseline value was > ULN) with the new appearance (i.e,. onset coincides with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or concomitant eosinophilia (> ULN)

8.6.2. Stopping Rules for Renal Function Test Results and Temporary Stopping Rules for Renal Function Test Results

Dosing should be stopped temporarily in the event of a persistent elevation that is observed over 2 consecutive weeks, for <u>any</u> of the 4 criteria below:

1. A decrease in $eGFR_{creat\text{-}cys}$ > 50% ($eGFR_{creat\text{-}cys}$ is calculated using the CKD-EPI creatinine-cystatin C equation [2012]).
2. $eGFR_{creat\text{-}cys}$ < 45 mL/min/1.73 m^2 (if Baseline $eGFR_{creat\text{-}cys}$ > 60 mL/min/1.73 m^2)
3. $eGFR_{creat\text{-}cys}$ < 30 mL/min/1.73 m^2 (if Baseline $eGFR_{creat\text{-}cys}$ ≤ 60 mL/min/1.73 m^2)
4. Proteinuria: Random UPCR > 5× Baseline AND > 1500 mg/g; or absolute UPCR value ≥ 2000 mg/g (confirmed by a repeat random spot UPCR ≥ 2000 mg/g or a 24 hr UPCR ≥ 2000 mg/24 hr)

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

If a dose is held, once $eGFR_{creat-cys}$ increases to ≥ 45 mL/minute/1.73 m^2, UPCR decreases to below 1000 mg/g, or the underlying cause of the decline in renal function is corrected, dosing may be reinitiated. In the case of UPCR of 2000 mg/g or higher, further evaluation for renal disease should be performed. If acute glomerulonephritis is confirmed, treatment should be permanently discontinued.

Dosing of a patient will be stopped permanently if urinalysis or renal blood tests confirm any of the following values in the absence of an alternative explanation agreed by a consulting nephrologist:

- urine protein is > 2 g (in 24-hour urine)
- 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

Please refer also to Table 4.

In the event of any platelet count less than 25 × 10^9/L, dosing of the patient with ION-682884 or inotersen will be stopped permanently. Platelet count should be monitored daily until 2 successive values above 25 × 10^9/L. Then monitor twice weekly until 3 successive values above 75 × 10^9/L. Then weekly monitoring until 3 successive values ≥100 × 10^9/L. Administration of steroids is recommended for patients whose platelet count is less than 50 × 10^9/L. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend dexamethasone 40 mg daily for 4 days every 2–4 weeks for 1-4 cycles; prednis(ol)one 0.5-2 mg/kg/d for 2–4 weeks then taper; or methylprednisolone 30 mg/kg/day for 7 days. (**Note:** Patient may require continuation with oral steroids after methylprednisolone.)

In the event of a platelet count < 75 × 10^9/L and ≥ 25 × 10^9/L, and in the absence of major bleeding (MB) or clinically relevant non-major bleeding (defined below), dosing with ION-682884 or inotersen should be suspended temporarily until the platelet count has recovered to ≥ 100 × 10^9/L. The suitability of the patient for continued dosing will be determined by the Investigator in consultation with the Study Medical Monitor and will be based on factors such as the original rate of decline in the patient's platelet count, whether any bleeding events were experienced, and the speed of recovery of platelet count after interruption of dosing. Treatment should be held if there is no evaluable platelet count within 14 days ±7 days prior to the scheduled dose. Any unreportable platelet count result must be rechecked and determined not to have met a stopping rule before dosing can continue.

Definition of Major Bleeding Events (Schulman and Kearon 2005)

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

Definition of Clinically Relevant Non-Major Bleeding Events

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

Definition of Minor Bleeding Events

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

Table 4: Actions in Patients with Low Platelet Count

If the subsequent test confirms the initial test result, then monitoring frequency and dosing should be adjusted as recommended in the table. Platelet monitoring and other safety actions apply to both treatment arms (ION-682884 and inotersen) as indicated below.

Platelet Count ($\times 10^9$/L)	**Platelet Monitoring Frequency and Other Safety Actions**	**Dosing**
≥ 125	Once every 4 weeks in ION-682884 treated patients. Once every 2 weeks in inotersen-treated patients and for 8 weeks after the last dose.	ION-682884: Every-4-weeks dosing should be continued. Inotersen: Weekly dosing should be continued
≥ 100 to < 125	Once every 2 weeks in ION-682884 treated patients. Once every 2 weeks in inotersen-treated patients and for 8 weeks after the last dose.	Continued dosing of ION-682884 every-4-weeks or inotersen weekly at Investigator's discretion.
≥ 75 to < 100	Once every week. Additional lab testing maybe performed per Section 8.5.3.	For both treatment arms: dosing should be paused until 3 successive values ≥ 100×10^9/L; on re-initiation of treatment, dosing frequency can be reduced per Investigator judgment in discussion with the Medical Monitor.
≥ 50 to < 75	Twice weekly until 3 successive values above 75×10^9/L then weekly monitoring. Additional lab testing maybe performed per Section 8.5.3. Seek expert hematology consultation.	For both treatment arms: dosing should be paused until 3 successive values > 100×10^9/L; on re-initiation of treatment, dosing frequency can be reduced per Investigator judgment in discussion with the Medical Monitor.
≥ 25 to < 50*	Twice weekly until 3 successive values above 75×10^9/L; then weekly monitoring until ≥.100 x 10^9/L then per Schedule of Procedures. Consider more frequent monitoring if additional risk factors for bleeding are present‡. Seek expert hematology consultation Corticosteroids should be considered. Consider discontinuation of any antiplatelet agents or anticoagulants. Additional lab testing maybe performed per Section 8.5.3. **Note: if a patient's platelet count falls to < 50×10^9/L, the Investigator must communicate to the Sponsor within 24 hours of receiving the platelet result**	For both treatment arms: dosing should be paused until 3 successive values > 100×10^9/L; on reinitiation of treatment dose should be reduced per Investigator judgment in discussion with the Medical Monitor.

Table 4: Actions in Patients with Low Platelet Count (Continued)

Platelet Count ($\times 10^9$/L)	Platelet Monitoring Frequency and Other Safety Actions	Dosing
< 25*	Daily until 2 successive values above 25 × 10^9/L. Then monitor twice weekly until 3 successive values above 75 × 10^9/L. Then weekly monitoring until stable. Seek expert hematology consultation Corticosteroids strongly recommended. Consider discontinuation of any antiplatelet agents or anticoagulants. Additional lab testing maybe performed per Section 8.5.3. **Note: if a patient's platelet count falls to < 50 × 10^9/L, the Investigator must communicate to the Sponsor within 24 hours of receiving the platelet result**	For both treatment arms: treatment should be permanently discontinued.

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

* It is strongly recommended that, unless corticosteroids are contraindicated, the patient receives glucocorticoid therapy to reverse the platelet decline as recovery in platelet count may be accelerated by administration of high-dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend dexamethasone 40 mg daily for 4 days every 2–4 weeks for 1–4 cycles; prednis(ol)one 0.5–2 mg/kg/d for 2-4 weeks then taper; or methylprednisolone 30 mg/kg/day for 7 days (note: may require continuation with oral steroids after methylprednisolone)

8.6.4. Stopping Rule for Ocular Effects

A patient should be permanently discontinued from Study Drug administration if they demonstrate clear signs of vitamin A deficiency confirmed by an ophthalmologist and discussed with the Investigator**.**

8.7. Adjustment of Dose and/or Treatment Schedule

No dose adjustment is planned, other than for safety reasons. Any proposed adjustment to treatment schedule or dose level must be discussed with 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 AEs ideally after consultation with the Study Medical Monitor. Minimally, Study Medical Monitor should be notified of all dosing changes.

8.8. Discontinuation of ION-682884 or Inotersen Treatment

The reasons for permanently discontinuation of Study Drug administration are:

- Patient request (no consent withdrawal for study participation)
- Patient withdrawal of consent for study participation

- Protocol specific requirements
  - The patient becomes pregnant. Report the pregnancy according to instructions in Section 9.5.4
  - The patient presents laboratory test abnormalities that meet any of the stopping rules listed in Sections 8.6.1 to 8.6.4
  - The patient receives major organ transplantation
- Investigator decision (e.g., AE, non-compliant patient)
- Sponsor decision

The reason for discontinuation of ION-682884 or inotersen must be recorded in the electronic Case Report Form (eCRF) and source documentation.

The Investigator will also work with patients and Sponsor to determine followup study visits and assessments after treatment termination. Ideally, patients who discontinue ION-682884 or inotersen treatment early will be encouraged to remain in the study and continue with protocol procedures and visits to collect efficacy endpoints and safety data. This is especially important for efficacy assessment on the landmark visits (Weeks 35, 66, 85, and 105).

Listed below is a guideline that can be used to determine which procedures should be performed depending on the patient's willingness for follow-up. Note that this will not account for all patient scenarios. Investigators are encouraged to contact the Medical Monitor to discuss each patient that will discontinue study treatment early. Variables such as length of time off drug, recent or current AEs including events described in Section 8.5 may result in modifications to the guidelines below.

1. Patient agrees to full follow-up
   - Complete the Early Termination Visit
   - Complete any required safety monitoring (see Sections 8.5 and 9.4)
   - Ensure patient has 20 weeks of safety follow-up after the last dose of ION-682884 or inotersen
   - Complete of all remaining study visits and procedures through Week 85 as well as survival status at Week 105
   - Update AE and Concomitant Medication information through last contact
2. Patient only agrees to targeted follow-up
   - Complete the Early Termination Visit
   - Complete any required safety monitoring (see Sections 8.5 and 9.4)
   - Return to the clinic to complete key efficacy assessments (serum TTR reduction, mNIS+7, Norfolk QOL-DN) on the landmark visits (Weeks 35, 66, 85, and 105)
   - Ensure patient has 20 weeks of safety follow-up after the last dose of ION-682884 or inotersen

- Update AE and Concomitant Medication information through last contact

3. Patient only agrees to survival status follow-up
   - Request that patient complete the Early Termination Visit
   - Request completion of any required safety monitoring (see Sections 8.5 and 9.4)
   - Collect data (e.g., AEs, concomitant medications, survival status) at Weeks 35, 66, 85, and 105 from one or more sources agreed to by patient (i.e., via correspondence/communication with patient, family/friends, other physicians, and/or from review of the medical records, as allowed per local laws and as stated in the IEC/IRB-approved ICF)

8.9. Discontinuation of Study Participation

The reasons for discontinuing patient participation in the study are:

- Patient withdrawal of consent for study participation
- At the discretion of the Investigator or Sponsor for noncompliance or significant protocol deviation

All efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. Reason for withdrawal from study must be recorded in the eCRF.

If consent is withdrawn, patient will be removed from further treatment and study observation immediately upon the date of request.

Withdrawal of consent by patient should be avoided as much as possible so that patient can be followed up in the trial for safety and efficacy. Ideally, attempts need to be made to complete landmark visits. Minimally, communication should be established with patients to obtain vital status at Weeks 35, 66, 85, and 105 by using the type of follow-up the patient is agreeable to: in person, by phone/mail, through family/friends, via correspondence/communication with other physicians, and/or from review of the medical records. The agreed means of follow-up will be documented in the patient records and notified to the Sponsor.

8.10. Concomitant Therapy and Procedures

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

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 and/or Sponsor. A patient may be allowed to substitute the Study Center provided vitamin A supplement with their own, only after consultation with the Study Medical Monitor.

Additional vitamin A supplements (other than those described above) are not allowed at any time during the study unless approved by the Study Medical Monitor (this includes multivitamin supplements that contain vitamin A).

Allowed Concomitant Therapy

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

Disallowed Concomitant Therapy

Concomitant therapy with the following drugs is not allowed: Vyndaqel® / Vyndamax™ (tafamidis), Tegsedi™ (inotersen), Onpattro™ (patisiran) or off-label use of diflunisal. Doxycycline short term use for the indication of infection (< 15 days) is allowed.

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 last study visit.

8.11. Treatment Compliance

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

Patients will record treatment in a dosing diary that will be reviewed periodically by Study Center staff and the Clinical Monitor.

9. SERIOUS AND NON-SERIOUS ADVERSE EVENT REPORTING

9.1. Sponsor Review of Safety Information

Safety information will be collected, reviewed, and evaluated by the Sponsor in accordance with the applicable Ionis and/or designee SOPs throughout the conduct of the clinical trial.

9.2. Regulatory Requirements

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

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

In addition to the Investigator's assessment of relatedness, the Sponsor will evaluate the available information and perform an independent assessment of all reported SAEs and determine if there is a reasonable possibility that the ION-682884 or inotersen is causally related to a reported SAE. While the Sponsor may upgrade an Investigator's decision it is not

permissible to downgrade the Investigator's opinion for the purposes of determining whether the SAE meets the definition of a SUSAR. If the event is considered by the Sponsor or designee to meet the definition of a SUSAR, the event will be reported.

For the purpose of regulatory reporting of SUSARs, there are no "expected" AEs in this study population.

9.3. Definitions

9.3.1. Adverse Event

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

An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)
- Recurrence of an intermittent medical condition (e.g., headache) not present at Baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from Study Drug or inotersen

9.3.2. Adverse Drug Reaction and Suspected Unexpected Adverse Drug Reaction

Adverse Drug Reaction (ADR)

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

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

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

Suspected Unexpected Adverse Drug Reaction

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

A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

9.3.3. Serious Adverse Event (SAE)

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

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

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

9.3.4. Adverse Event of Special Interest

Adverse events of special interest (AESI), including both serious or non-serious events, is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor could be appropriate.

Adverse events of special interest, if defined in the study protocol, are required to be reported by the Investigator to the Sponsor immediately, no more than 24 hours of the Investigator's first knowledge of the event.

For the purpose of this study, severe reductions in platelet count < 50×10^9/L accompanied by a MB or CRNMB, or platelet count of < 25×10^9/L independent of a MB or CRNMB event are considered as AEs of special interest and should be subject to 15-day expedited reporting by the Sponsor to the regulatory agencies.

9.4. Monitoring and Recording Adverse Events

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

9.4.1. Serious Adverse Events

In the interest of subject safety, and in order to fulfill regulatory requirements**,** all SAEs (regardless of their relationship to ION-682884 or inotersen) should be reported to the Sponsor within 24 hours of the Study Center's first knowledge of the event. The collection of SAEs will begin after the patient signs the informed consent form and stop at the end of the subject's Follow-up Period which is defined as the final study visit (Week 105 or last visit if patient early terminates). SAEs should be reported using an electronic SAE submission form within Electronic Data Capture (EDC) whenever possible. In situations where the electronic SAE submission via EDC is unavailable, an Initial Serious Adverse Event Form should be completed and a copy should be faxed or emailed to the Sponsor. The SAE reporting instruction, including the fax number and email address can be found in the Investigator site file for the study.

Detailed information should be actively sought and included on Follow-Up Serious Adverse Event Forms as soon as additional information becomes available. All SAEs will be followed until resolution. SAEs that remain ongoing past the 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 study visit (Week 105 or last visit if patient early terminates; Section 3.4.3). The Investigator will monitor each patient closely and record all observed or volunteered AEs on the Adverse Event Case Report Form.

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

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

9.4.3.1. Relationship to the use of ION-682884 or Inotersen

The event's relationship to ION-682884 or inotersen is characterized by 1 of the following:

- **Related:** There is clear evidence that the event is related to the use of ION-682884 or inotersen, 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 ION-682884 or inotersen 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 ION-682884 or inotersen 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 ION-682884 or inotersen

9.4.3.2. Severity

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

- **Mild:** The event is easily tolerated by the 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 9.3.2).

9.4.3.3. Action Taken with ION-682884 / Inotersen

Action taken with ION-682884 or inotersen due to the event is characterized by 1 of the following.

- **None:** No changes were made to treatment and dosing
- **Permanently Discontinued:** Treatment 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 on the Adverse Event Case Report Form. Treatment should also be recorded on the concomitant treatment or ancillary procedures eCRF, as appropriate.

9.4.3.5. Outcome of the Adverse Event

If the event is a non-serious AE, then the event's outcome is characterized by 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 a non-serious AE on the AE eCRF (the SAE resolution date should be entered as the date of onset of that AE)
- **Recovered:** Patient recovered completely from the SAE (the date of recovery should be entered as the SAE resolution date)
- **Recovered with Sequelae:** The signs/symptoms of the reported SAE have improved but not completely resolved, and a new Baseline for the patient is established since full recovery is not expected
- **Fatal:** Patient died (the date of death should be entered as the SAE resolution date)

9.4.3.6. Follow-up of Adverse Event

Investigator Follow-Up

During the Study Period, the Investigator should follow each AE until the event has resolved to Baseline grade or better, the event is assessed as stable, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to ION-682884 or inotersen, or related to study procedures until a final outcome can be reported.

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

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

Sponsor Follow-Up

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

9.5. Procedures for Handling Special Situations

9.5.1. Abnormalities of Laboratory Tests

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

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

9.5.2. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

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

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

9.5.3. Dosing Errors

ION-682884 or inotersen errors (including overdose, underdose, and administration error) should be documented as Protocol Deviations, subcategory Dosing Error. A brief description should be provided in the deviation, including whether the patient was symptomatic (list symptoms) or asymptomatic, and the event accidental or intentional.

Dosing details should be captured on the Dosing Case Report Form. If the patient takes a dose of ION-682884 or inotersen 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.

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an AE, but it may result in an AE. Any overdose or incorrect administration of ION-682884 or inotersen should be noted on the Study Drug Administration eCRF. All AEs associated with an overdose or incorrect administration of ION-682884 or inotersen should be recorded on the Adverse Event eCRF. If the associated AE fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

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

9.5.4. Contraception and Pregnancy

Male patients and female patients of child-bearing potential must continue to use appropriate highly effective 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 **within 24 hours** of first learning of the occurrence of pregnancy. Follow-up information including delivery or termination is reported by designating as 'Follow-up' on the Pregnancy Forms and reported within 24 hours.

Payment for all aspects of obstetrical care, child or related care will be the 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 ION-682884 or inotersen. However, the patient will be encouraged to complete the post-treatment follow-up portion of the study to the extent that study procedures do not interfere with the pregnancy. Regardless of continued study participation, the study physician will assist the patient in getting obstetrical care and the progress of the pregnancy will be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the Study Center and Sponsor may require access to the mother and infant's medical records to obtain additional information relevant to the pregnancy progress and outcome. A longer follow-up may be required if a newborn child experiences a medical condition. Follow-up will be performed to the extent permitted by the applicable regulations and privacy considerations; e.g., pregnancy ICF may be required.

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

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

10. STATISTICAL CONSIDERATIONS

10.1. Study Endpoints

Study endpoints are described in Section 1.2.

10.2. Sample Size Considerations

The sample size for this study was estimated based on the data from the NEURO-TTR clinical trial.

With 140 patients (120 of them dosed with ION-682884) and assuming a 10% dropout rate, there would be 108 evaluable patients treated with ION-682884. In the NEURO-TTR trial, there are 52 evaluable placebo patients.

It is observed that the NEURO-TTR placebo group had a 23.8 point increase in the mNIS+7 score from Baseline to Week 66. It is estimated that the ION-682884 group will have a 4.2 point increase in mNIS+7. The standard deviation of the change from Baseline is estimated to be 20. There would be at least 90% power to detect a 19.6 point difference in the change from Baseline of the mNIS+7 score between ION-682884-treated patients and the NEURO-TTR-placebo patients, with a 2-sided alpha level of 0.025.

For the Norfolk QOL-DN, it is observed that the NEURO-TTR placebo group had 10.7 points change from Baseline to Week 66. It is estimated that the ION-682884-treated group will have a 0 point change from Baseline. The standard deviation is estimated to be 20. There would be at least 80% power to detect a 10.7 points difference in the change from Baseline of the Norfolk QOL-DN between ION-682884-treated patients and the NEURO-TTR placebo patients, with a 2-sided alpha level of 0.025.

For the TTR percent change from Baseline, it is observed that the NEURO-TTR placebo group had 9.7% reduction from Baseline to Week 65. It is estimated that the ION-682884-treated group will have at least 80% reduction from Baseline. The standard deviation is estimated to be 13%. There would be at least 95% power to detect a 70.3% difference in the percent change from Baseline between ION-682884-treated patients and the NEURO-TTR-placebo patients, with a 2-sided alpha level of 0.025.

10.3. Populations

The population definitions that will be used in this study are provided below and are very similar to those employed in the NEURO-TTR trial.

Full Analysis Set: All randomized patients who received at least 1 injection of ION-682884 or inotersen and who have a Baseline and at least 1 post-Baseline efficacy assessment for mNIS+7

score or Norfolk QOL-DN questionnaire total score. For NEURO-TTR trial, the Full Analysis Set includes all randomized patients who received at least 1 injection of Study Drug (inotersen or placebo) and who have a Baseline and at least 1 post-Baseline efficacy assessment for the mNIS+7 score or Norfolk QOL-DN questionnaire total score.

Per Protocol Set: A subset of Full Analysis Set who received at least a certain percentage of the prescribed doses of ION-682884 and that have no significant protocol deviations that would be expected to affect efficacy assessments. The detailed criteria will be specified in the SAP. For NEURO-TTR trial, the Per-Protocol Set includes the subset of the NEURO-TTR Full Analysis Set who have received at least 80% of the prescribed doses of Study Drug (inotersen or placebo) and who have no major protocol violations that would be expected to affect efficacy assessments.

Safety Set: All patients who are randomized and receive at least 1 dose of ION-682884 or inotersen. For NEURO-TTR trial, the Safety Set includes all randomized patients who received at least 1 injection of Study Drug (inotersen or placebo).

PK Population: All patients who are randomized and receive at least 1 dose of ION-682884 or inotersen and have at least 1 evaluable PK sample.

10.4. Definition of Baseline

The same Baseline definitions from the NEURO-TTR trial will be applied in this study. The Baseline for efficacy, PD and safety assessments will be defined as follows:

- Baseline mNIS+7 and its individual components will be defined as the average of 2 assessments taken within 60 days prior to the first dose of ION-682884 or inotersen. If only one assessment has been done, the single assessment will be used in place of the average. Rarely, for patient convenience, the Baseline mNIS+7 assessment(s) (or a subset of this assessment) will have been completed early in the Treatment Period rather than pre-treatment. These will be considered protocol deviations. These assessments will be included in the analysis as valid Baseline assessments provided they are taken within 1 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 primary analysis.
- Baseline NSC and individual components will be defined as the average of 2 assessments taken within 60 days prior to the first dose of ION-682884 or inotersen. If only 1 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, it is possible it could be completed early in the Treatment Period rather than pre-treatment. These will be considered protocol deviations. These assessments will be included in the analysis as valid Baseline assessments, provided they are taken within 1 week after the first dose.
- Baseline ECG will be defined as the average of the triplicate taken on Day 1 pre-dose. If only 1 or 2 assessments are available, the single assessment or average of the 2 assessments will be used. If the case that Day 1 pre-dose ECG is missing, screening visit results will be used as Baseline.

- Baseline laboratory assessment including PD will be defined as the average of all non-missing pre-dose assessments.

Baseline for all other assessments will be defined as the last non-missing value prior to the first dose of study drug (ION-682884 or inotersen).

10.5. Interim Analysis and Multiplicity

An interim analysis will be performed to assess the efficacy and safety profile of ION-682884 comparing to the placebo arm of Neuro-TTR when all patients on ION-682884 complete Week 35 assessments.

Week 35 Interim Analysis

The multiplicity will be controlled by using the ranking strategy in the following testing sequence:

- Interim Analysis PEP. Comparison of percent change from Baseline to Week 35 in the TTR between ION-682884 and NEURO-TTR placebo in the Full Analysis Set.
- Interim Analysis PEP. Comparison of change from Baseline to Week 35 in the mNIS+7 between ION-682884 and NEURO-TTR placebo in the Full Analysis Set.
- Interim Analysis Secondary Endpoint. Comparison of change from Baseline to Week 35 in the Norfolk total score between ION-682884 and NEURO-TTR placebo in the Full Analysis Set.

The statistical analysis will be conducted with 2-sided alpha level of 0.025. If any of the endpoint is not statistically significant, the remaining test(s) will not be conducted in the interim analysis.

Week 66 Final Analysis

The multiplicity for the final analysis will be controlled by using the ranking strategy in the following testing sequence:

- Co-Primary Endpoint: Comparison of percent change from Baseline to Week 65 in the TTR between ION-682884 and NEURO-TTR placebo in the Full Analysis Set
- Co-Primary Endpoint: Comparison of change from Baseline to Week 66 in the mNIS+7 between ION-682884 and NEURO-TTR placebo in the Full Analysis Set
- Co-Primary Endpoint: Comparison of change from Baseline to Week 66 in the Norfolk total score between ION-682884 and NEURO-TTR placebo in the Full Analysis Set
- Secondary Endpoint: Comparison of change from Baseline to Week 66 in the NSC between ION-682884 and NEURO-TTR placebo in the Full Analysis Set
- Secondary Endpoint: Comparison of change from Baseline to Week 35 in the NSC between ION-682884 and NEURO-TTR placebo in the Full Analysis Set
- Secondary Endpoint: Comparison of change from Baseline in the PCS score of SF-36 at Week 65 between ION-682884 or NEURO-TTR placebo in the Full Analysis Set

- Secondary Endpoint: Comparison of change from Baseline to Week 65 in the PND between ION-682884 and NEURO-TTR placebo in the Full Analysis Set
- Week 66 Final Analysis Secondary Endpoint: Comparison of change from Baseline to Week 65 in mBMI between ION-682884 and NEURO-TTR placebo in the Full Analysis Set

In the Week 66 Final Analysis, for those statistically significant endpoints at Week 35 Interim Analysis, their corresponding tests at the Week 66 Final Analysis will not be conducted in the ranking strategy for multiplicity. The first test will be for the endpoint which is not statistically significant at the Week 35 Interim Analysis. The alpha level for this endpoint will be determined by the resampling procedure (Westfall and Young 1993) as follows.

Let T1 and T2 be the standardized test statistics at the interim and final analyses, respectively. In order to determine the alpha level for the final analysis, the correlation between T1 and T2 is first estimated based on the resampling approach:

- Among the 108 ION-682884 treated patients and 52 NEURO-TTR placebo patients, randomly assign 108 patients to the ION-682884 treated group and 52 patients to NEURO-TTR placebo group
- Apply the re-randomized treatment assignment to the interim data and obtain the standardized test statistics T1
- Apply the re-randomized treatment assignment to the final data and obtain the standardized test statistics T2

Repeat the above procedure N times (N = 10000) and obtain N pairs of test statistics T1 and T2. The correlation between T1 and T2 will then be estimated as the sample correlation of the N pairs.

Let c1 be the cut-off point for the interim 2-sided test corresponding to an alpha of 0.025. Once the estimated correlation ρ is available, the cut-off point c2 for the final analysis is obtained by solving the nonlinear equation $Pr(|T1| \geq c1 \text{ or } |T2| \geq c2) = 0.05$, where (T1, T2) follow a bivariate normal distribution with mean vector (0, 0), standard deviations of 1 and correlation ρ.

For those endpoints that are not tested in the interim analysis, significant level of 0.05 will be used in the final analysis.

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 (25^{th} percentile, 75^{th} percentile), and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data by treatment group. Where appropriate, p-values will be reported. All statistical tests will be conducted using 2-sided tests with 5% Type I error rates unless otherwise stated.

All primary, secondary and PD 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.

The reference arm (inotersen) will be summarized descriptively and no statistical comparison will be made between the reference arm and the ION-682884-treated arm.

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. Efficacy Analysis

10.6.2.1. Primary Analysis

10.6.2.1.1. Primary Analysis at Interim Analysis

Below are the 2 primary analyses for interim analysis

- Comparison of percent change from Baseline to Week 35 in the TTR between ION-682884 and NEURO-TTR placebo in the Full Analysis Set
- Comparison of change from Baseline to Week 35 in the mNIS+7 between ION-682884 and NEURO-TTR placebo in the Full Analysis Set

The percent change in TTR from Baseline to Week 35 will be analyzed using the Mixed Effects Model with Repeated Measures (MMRM) model adjusted by propensity score weights. The MMRM model will also include the effects of treatment (ION-682884 or NEURO-TTR placebo), time (categorical), disease stage (Stage 1/Stage 2), V30M mutation (Yes/No), previous treatment (Yes/No), treatment-by-time interaction, baseline value of the endpoint, and the baseline-by-time interaction. The propensity score will be calculated for each NEURO-TTR placebo or ION-682884 patient using a logistic regression model with Baseline covariates including disease stage (Stage 1/Stage 2), V30M mutation (Yes/No), and previous treatment (Yes/No).

The second PEP mNIS+7 is scheduled to be assessed at Week 35, Week 66, and Week 85. Because only 1 post-Baseline assessment (Week 35) is available at Week 35 Interim Analysis, the treatment comparison at Week 35 will be based on the analysis of covariance (ANCOVA) model adjusted by propensity score. The ANCOVA model will also include the effects of treatment (ION-682884 or NEURO-TTR placebo), disease stage (Stage 1/Stage 2), V30M mutation (Yes/No), previous treatment (Yes/No), and the Baseline value of the endpoint. Patients with a missing mNIS+7 at Week 35 will have value multiply imputed using an imputation model that contains the following variables: disease stage (Stage 1/Stage 2), V30M mutation (Yes/No), previous treatment (Yes/No), and the Baseline value of the endpoint and the multiple imputation will be stratified by treatment group (Schafer 1997; Schafer 1999). Any patient who discontinues early from the Treatment Period will be strongly encouraged to complete landmark assessments.

10.6.2.1.2. Primary Analysis at Week 66 Final Analysis

For percent change from Baseline of TTR at Week 65, change from Baseline of mNIS+7 at Week 66, and change from Baseline of Norfolk QOL-DN at Week 66, MMRM model adjusted by propensity score weights will be used.

10.6.2.2. Secondary Analysis

10.6.2.2.1. Secondary Analysis at Interim Analysis

The secondary analysis at interim analysis is the comparison of change from Baseline to Week 35 in the Norfolk total score between ION-682884 and NEURO-TTR placebo in the Full Analysis Set. The analysis will be conducted in the same way as for the mNIS+7 in the Week 35 Interim Analysis.

10.6.2.2.2. Secondary Analysis at Final Analysis

The secondary endpoints at Week 66 Final Analysis include the following analyses:

- Comparison of change from Baseline to Week 66 in the NSC between ION-682884 and NEURO-TTR placebo in the Full Analysis Set
- Comparison of change from Baseline to Week 35 in the NSC between ION-682884 and NEURO-TTR placebo in the Full Analysis Set
- Comparison of change from Baseline in the PCS score of SF-36 at Week 65 between ION-682884 or NEURO-TTR placebo in the Full Analysis Set
- Comparison of change from Baseline to Week 65 in the PND between ION-682884 and NEURO-TTR placebo in the Full Analysis Set.
- Comparison of change from Baseline to Week 65 in mBMI between ION-682884 and NEURO-TTR placebo in the Full Analysis Set

The secondary analyses will be conducted in the same way as for the primary analysis at Week 66 Final Analysis.

10.6.2.3. Pharmacodynamic Analysis

Pharmacodynamic analyses include comparisons of change from Baseline in TTR between ION-682884 and NEURO-TTR placebo group. The data will be analyzed in the same way as for the PEP at Week 66 Final Analysis.

10.6.2.4. Exploratory Analyses

Exploratory analysis includes the comparisons of change from Baseline in ECHO parameters, at Week 66 and NT-proBNP at Week 65 between ION-682884 or the NEURO-TTR placebo group. Additional analyses on the all cause hospitalizations in all patients at Week 66, all cause hospitalizations in patients with cardiac involvement at Week 66, mNIS+7 and Norfolk QOL-DN at Week 85, 10MWT, R-ODS, COMPASS-31 and EQ-5D-5L at Weeks 37 and 81 will be provided. PGIS and PGIC will be assessed for purposes of psychometric analyses of selected

clinical outcome assessment measures. Details of exploratory analyses will be provided in the SAP.

10.6.3. Pharmacokinetic and Immunogenicity Analysis

10.6.3.1. Pharmacokinetic Analysis

Noncompartmental PK analysis of ION-682884 (as total full-length oligonucleotides, including fully, partially, and un-conjugated ION-682884) or inotersen will be carried out on each individual patient data set in the PK subgroup where limited intensive plasma PK samples are collected following the dose on Days 1, 225, and 449. The maximum observed drug concentration (C_{max}) and the time taken to reach C_{max} (T_{max}) will be obtained directly from the concentration-time data. Partial areas under the plasma concentration time- curve from time zero (pre-dose) to the last observable concentration (AUC_{0-t}) after SC administration will be calculated using the linear-up logdown- trapezoidal method.

For all evaluable patients receiving ION-682884 or inotersen, plasma drug concentrations during the Treatment Period and at the Post-Treatment Follow-Up Period will be listed by treatment, dose, study day, time point, patient ID, patient anti-drug antibody (ADA) status, and summarized using descriptive statistics, with and without stratification by patient immunogenicity status. The apparent plasma terminal elimination half-life of ION-682884 or inotersen following the last administered dose will be calculated in each evaluable patient with post-treatment PK samples collected (when deemed possible by the PK scientist).

Plasma PK parameters will be summarized using descriptive statistics, with and without stratification by patient immunogenicity status. Other PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist. Additional details regarding the PK analysis will be described in the SAP.

Potential relationships between selected PD and plasma exposure measures (e.g., trough concentrations) may also be explored, where deemed appropriate.

10.6.3.2. Immunogenicity Analysis

ADA will be determined in a multi-tiered approach that includes screening, confirmation, and titration (if confirmed positive) assays at Baseline, during treatment, and at the end of Follow-Up Period for all patients (receiving either ION-682884 or inotersen) in the study. Immunogenicity results (screen positive/negative, confirmed positive/negative or not evaluable, and when applicable, titer of ADA) before, during, and after treatment with ION-682884 or inotersen (i.e., sample ADA status) will be listed. Patient ADA status (positive/negative or not evaluable) for all evaluable patients, along with the study day that the first positive immunogenicity status emerged (T_{first}, i.e., onset of ADA development), the last positive immunogenicity status observed (T_{last}), the last ADA sample collection day, and peak titer if applicable, will be listed by their treatment and study day. Patients with positive ADA status may be further classified (where applicable) as being either ‘persistent’, ‘transient’, or ‘not determinable’, if deemed appropriate.

Additionally, the sample and patient immunogenicity incidence (number) and incidence rate (percent) will be summarized as the total number and percent of evaluated patients with antibody

negative, positive, and unknown status by treatment and dose. Furthermore, onset, titer over time, and peak titer of the ADA response, if applicable, will be summarized as median, quartiles (25% and 75%), and range by treatment and dose.

Potential effect of immunogenicity on efficacy and safety will be evaluated. Additional details regarding the IM data analysis will be described in the SAP.

10.6.4. Safety Analysis

Treatment duration and amount of ION-682884 or inotersen received will be summarized by treatment group, as well as reasons for any withdrawals from ION-682884 or inotersen.

All treatment-emergent adverse events (AEs with onset after the first dose of ION-682884 or inotersen) and SAEs will be summarized for each treatment group using the MedDRA™ coding system, by system organ class, preferred term, relationship to ION-682884 or inotersen, and severity. Narratives of deaths, SAEs, including early withdrawals from ION-682884 or inotersen and from study due to AEs, will also be provided.

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

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

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 ION-682884 or inotersen are administered. The patient must be given sufficient time to consider whether to participate in the study. The informed consent may be administered remotely using locally accepted methods.

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

All applicable regulations and guidelines of current Good Clinical Practice (GCP) as well as the demands of national drug and data protection laws and other applicable regulatory requirements must be followed.

11.3. Independent Ethics Committee (IEC)/Institutional Review Board (IRB)

A copy of the protocol, proposed informed consent form, other written patient information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by the Sponsor before recruitment of patients into the study and shipment of ION-682884 or inotersen. 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 ION-682884 or inotersen. 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. The Investigator should also notify the IEC/IRB of SAEs occurring at the Study Center and other AE reports received from the Sponsor, in accordance with local procedures.

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

11.4. Patient Confidentiality

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

In compliance with Federal and local regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the 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 IRB/IEC 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 IRB/IEC to the Sponsor.

12.2. Study Termination

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

12.3. Study Documentation and Storage

An electronic case report form (eCRF) utilizing an EDC application will be used for this study.

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

Source documents are original documents, data, and records from which the patient's case report form data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, imaging, and correspondence.

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

- Patient files containing completed case report forms, informed consents, and supporting copies of source documentation
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation and all correspondence to and from the IRB/IEC and the Sponsor
- If drug supplies are maintained at the Study Center, proof of receipt, ION-682884 or inotersen Product Accountability Record, Return of ION-682884 or inotersen Product for Destruction, final ION-682884 or inotersen product reconciliation, and all drug-related correspondence

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

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

12.4. Study Monitoring

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

The Sponsor will be blinded for mNIS+7 and Norfolk-QOL-DN throughout the study, to decrease bias in the conduct of the study.

The Sponsor monitor is responsible for inspecting the case report forms at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to patient medical records and other study-related records needed to verify the entries on the case report forms. The access to these records may include viewing your medical records remotely, from a location outside of the study center (where allowed locally).

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

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

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

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

12.5. Language

Case report forms must be completed in English. Generic names and trade names are acceptable for concomitant medications. Combination medications should be recorded using their trade name.

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

12.6. Compensation for Injury

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

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14. APPENDICES

APPENDIX A. SCHEDULE OF PROCEDURES

Appendix A Schedule of Procedures

Shaded columns denote mandatory in-Clinic visits

Day 1 – Week 35

	Screening Period[7]	Baseline Assessments[1]	Treatment Period[2]																	
Study Week	-10 to -1		1	3	5[14]	7	9[14]	11	13	15	17	19	21	23	25	27	29	31	33[14]	35
Study Day	-70 to-2		1	15	29	43	57	71	85	99	113	127	141	155	169	183	197	211	225	239
Visit Window (days) (±)	0	0	0	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	10
Mandatory in-Clinic Visit	X	X	X						X						X					X
Mandatory Discussion (face-to-face or phone call)					X		X												X	
Informed Consent	X																			
Eligibility Criteria	X																			
Medical History	X																			
Physical Exam[3]	X		X						X						X					X
Vital Signs (BP, HR, RR, temperature)	X		X						X						X				X	X
Height			X																	
Body Weight			X						X											X
ECG (12-lead)	X[15]								X											X
NIS	X																			
mNIS+7[4]		2X																		X
Norfolk QOL-DN[4]			X																	X
PND Score, SF-36			X																	X
10MWT, R-ODS, COMPASS-31, EQ-5D-5L			X																	
PGIS			X																	
Ocular Questionnaire			X						X						X				X	
Transthoracic ECHO[5]		X																		X
TTR Genotyping[6]	X																			
Screening Labs[7]	X																			
Pregnancy Test[8]	X		X	X		X		X		X		X		X		X		X		X
Chemistry, Hematology and Urinalysis[9]	X		X						X						X					
Abbreviated Monitoring Panel[9]				X		X		X		X		X		X		X		X		X
Platelets, eGFR, UPCR, LFTs (Only patients receiving inotersen)[16]			Every 2 Weeks Except when Chemistry, Hematology and Urinalysis or Abbreviated Monitoring Panels are Drawn →																	
NT-proBNP, Troponin T, CK-MB			X						X											X
TSH with reflexive FT4 and TT3	X		X						X						X					
Serum Vitamin A[10]	X		X						X						X					
Retinyl Palmitate (fasting)			X						X						X					

Appendix A Schedule of Procedures Continued

Day 1 – Week 35 Continued

	Screening Period[7]	Baseline Assessments[1]	Treatment Period[2] Continued																	
Study Week	-10 to -1		1	3	5[14]	7	9[14]	11	13	15	17	19	21	23	25	27	29	31	33[14]	35
Study Day	-70 to-2		1	15	29	43	57	71	85	99	113	127	141	155	169	183	197	211	225	239
Visit Window (days) (±)	0	0	0	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	10
Mandatory in-Clinic Visit	X	X	X						X						X					X
Mandatory Discussion (face-to-face or phone call)					X		X												X	
Serum TTR, Neurofilament Light Chain, Neurofilament Heavy Chain, Coagulation and Immunoglobulins	X		X						X						X					X
PK Blood Sampling (for more details please review Appendix C)			X[a,b]		X[a]				X[a]						X[a]				X[a,b]	X
Inflammatory Panel			X																	X
Immunogenicity Testing			X		X				X										X	
Archived Serum/Plasma Samples[11,12]			X		X		X		X										X	X
ION-682884 Administration[13]			X		X		X		X		X		X		X		X		X	
Inotersen Administration[13]			Every Week until Week 34 (inclusive) →																	
Adverse Events	X		Monitor continuously →																	
Concomitant Medications	X		Monitor continuously →																	

Appendix A Schedule of Procedures Continued

Week 37 – Week 85

	Treatment Period[2]																								EOT
Study Week	**37**	**39**	**41**	**43**	**45**	**47**	**49**	**51**	**53**	**55**	**57**	**59**	**61**	**63**	**65**	**66**	**67**	**69**	**71**	**73**	**75**	**77**	**79**	**81**	**83**	**85**
Study Day	**253**	**267**	**281**	**295**	**309**	**323**	**337**	**351**	**365**	**379**	**393**	**407**	**421**	**435**	**449**	**456**	**463**	**477**	**491**	**505**	**519**	**533**	**547**	**561**	**575**	**EOT 589**
Visit Window (days) (±)	**10**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**10**	**10**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**
Mandatory in-Clinic Visit	**X**						**X**				**X**				**X**	**X**				**X**				**X**		**X**
Physical Exam[3]							X								X					X						X
Vital Signs (blood pressure, heart rate, respiratory rate, temperature)	X						X				X				X					X				X		X
Body Weight											X				X											X
ECG (12-lead)															X											X
mNIS+7[4]																2X										X
Norfolk QOL-DN[4]																X										X
PND Score, SF-36															X											X
10MWT, R-ODS, COMPASS-31, EQ-5D-5L	X																							X		
PGIS, PGIC	X																									X
Ocular Questionnaire	X						X				X				X					X						X
Transthoracic ECHO[5]																X										X
Pregnancy Test[8]	X	X		X		X		X		X		X		X			X		X		X		X			X
Chemistry, Hematology and Urinalysis [9]	X						X				X				X					X				X		X
Abbreviated Monitoring Panel[9]		X	X	X		X		X		X		X		X			X		X		X		X		X	
NT-proBNP, Troponin T, CK-MB															X											X
TSH with reflexive FT4 and TT3	X						X								X											X
Serum Vitamin A[10]	X						X								X											X
Retinyl Palmitate (fasting)	X						X								X											X
Serum TTR, Neurofilament Light Chain, Neurofilament Heavy Chain, Immunoglobulins, and Coagulation							X				X				X					X				X		X
PK Blood Sampling (for more details please review Appendix C)							X[a]				X[a]				X[a,b]	X				X[a]				X[a]		X
Inflammatory Panel															X											X
Immunogenicity Testing							X								X											X
Archived Serum/Plasma Samples[11,12]	X						X				X				X	X				X				X		X
ION-682884 Administration[13]	X		X		X		X		X		X		X		X			X		X		X		X		
Adverse Events	Monitor continuously →																									
Concomitant Medications	Monitor continuously →																									

Appendix A Schedule of Procedures Continued

Post-Treatment Evaluation Period and Early Termination Visit

	Post-Treatment Evaluation Period					Early Termination / ET
Study Week	**89**	**93**	**97**	**101**	**105**	
Study Day	**617**	**645**	**673**	**701**	**729**	
Visit Window (days) (±)	7	7	7	7	7	
Mandatory In-Clinic Visit		**X**			**X**	**X**
Physical Exam[3]		X			X	X
Vital Signs (BP, HR, RR, temperature)		X			X	X
Body Weight		X			X	X
ECG (12-lead)					X	X
mNIS+7[4]					X	2X
Norfolk QOL-DN[4]					X	X
PND Score, SF-36					X	X
10MWT, R-ODS, COMPASS-31, EQ-5D-5L					X	X
PGIS, PGIC					X	X
Ocular Questionnaire		X			X	X
Transthoracic ECHO[5]					X	X
Pregnancy Test[8]	X	X	X	X	X	X
Chemistry, Hematology and Urinalysis [9]	X	X	X		X	X
NT-proBNP, Troponin T, CK-MB		X			X	X
Abbreviated Monitoring Panel[9]						
TSH with reflexive FT4 and TT3					X	X
Serum Vitamin A[10]		X			X	X
Retinyl Palmitate (fasting)		X			X	X
Serum TTR, Neurofilament Light Chain, Neurofilament Heavy Chain, Immunoglobulins and Coagulation		X			X	X
PK Blood Sampling (for more details please review Appendix C)		X			X	X
Inflammatory Panel					X	X
Immunogenicity Testing					X	X
Archived Serum/Plasma Samples[11,12]		X			X	X
Adverse Events			X			X
Concomitant Medications			X			X

S = Screening Day, D = Day, W = Week

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

Visits that are not mandated to be in-clinic can be completed either: in-clinic; at home by a home health-care provider (if approved locally); or using a laboratory local to the patient upon Investigator approval. Additionally, if needed per Investigator judgment with Medical Monitor consultation, local laboratory studies can be performed for patient safety and trial compliance.

Legend

[1] Baseline assessments should only be done once a patient is considered eligible to participate in the study

[2] During in-clinic visits, ION-682884 or inotersen can be administered in the clinic, after conducting all procedures scheduled for that day (except for post-dose PK sampling; for details please review Appendix C). Alternatively, ION-682884 or inotersen can be administered at home by the patient/caregiver after clinic visits (except for PK Subgroup on days with post-dose PK sampling; for details please review Appendix C). Patients who discontinue ION-682884 or inotersen treatment early will be encouraged to remain in the study and continue with protocol procedures and visits to collect efficacy endpoints and safety data. For details review Section 8.8.

Appendix A Schedule of Procedures Continued

Legend Continued

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

[4] The mNIS+7 assessment procedure includes: NIS, QST, HRDB and pre-determined sensory and nerve conduction testing. Additional clinical evaluations done during mNIS+7 assessment include: Lower Limbs Function Test (LLF) and NSC. Two (2) independent mNIS+7 assessments will be performed at selected visits on separate days. Both Baseline mNIS+7 assessments should be performed within 21 days prior to the first dose of ION-682884 or inotersen (Day 1). In addition, every effort should be made to conduct the 2 assessments < 7 days apart.

For an individual patient, every effort should be made to use the same mNIS+7 evaluator throughout the study and the evaluator must be insulated from the patient's general study procedures and knowledge of the patient's AEs. Norfolk QOL-DN must be administered prior to any other study procedures. At Baseline and Week 66, the Norfolk QOL-DN can be administered on the same day as the first mNIS+7 assessment.

[5] Transthoracic ECHO can be completed with ± 21-day window around Week 35, 66, 85 and 105 visits.

[6] For determination of patient eligibility only if appropriate documentation is not available.

[7] Screening Labs include FSH (for confirmation of menopause as per Inclusion Criteria 3 ii), HIV, HBV and HCV, SPEP and UPEP with immunofixation, serum free light chain ratio, and HbA1C per Appendix B.

[8] Conducted only in women who are of child-bearing potential per Inclusion Criterion 3 iv. Pregnancy test should be conducted on serum or plasma samples at Screening and during in-clinic visits. During visits at home, pregnancy test can be conducted on urine or serum/plasma. However, on Day 1, pregnancy test should be conducted by urine as well as serum/plasma so that a negative urine test is available prior to dosing.

[9] If chemistry, hematology or urinalysis results are uninterpretable (e.g., due to clumping, hemolysis or quantity not sufficient) or missing, a repeat sample should be collected as soon as possible (ideally within 7 days). The window for sample collections that occur outside clinic visits is ± 4 days. See Section 8.5 for guidance on ION-682884 or inotersen dosing relative to chemistry, hematology or urinalysis monitoring. After the last dose (Week 81), monitoring should be performed every 4 weeks for 8 weeks (until Week 89, inclusive), either by Chemistry, Hematology or Urinalysis panel or by Abbreviated Monitoring panel.

[10] Collection of laboratory samples for vitamin A/Retinol testing should precede the ingestion of vitamin A supplement for that day.

[11] Stored at least at -70 °C for follow-up exploration of PD, laboratory findings (including disease biomarkers not specified in this protocol) and/or AEs (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.) in this or subsequent clinical studies of ION-682884.

[12] The collection of the blood sample for potential follow up exploration of laboratory findings, AE, or disease progression in this or subsequent clinical studies of ION 682884 (not for genetic research) is expected for all patients, collection can only proceed if supported by local regulations and after patient consent

[13] The window of drug administration is ± 1 week for ION-682884, and ± 4 days for inotersen.

[14] On Weeks 5, 9, and 33, in-clinic visits are encouraged but not mandated. If in-clinic visit is not done, Investigator must communicate with patients by phone or telemedicine tools where available to go over concomitant medications, AEs/SAEs and their general health. Physical exam may be skipped per Investigator judgment. A home health care provider can collect lab samples, VS, and ensure proper dosing of the Study Drug. If not in-clinic, PK and immunogenicity samples may be skipped. If patient is part of PK subset, then Week 33 is mandatory to be in-clinic.

[15] ECG before first dose can be performed and assessed by Investigator anytime between Screening up to Day 1 visit as long as it is performed before the first dose.

[16] If results are uninterpretable (e.g., due to clumping, hemolysis or quantity not sufficient) or missing, a repeat sample should be collected as soon as possible (ideally within 7 days). The window for sample collections that occur outside clinic visits is ± 4 days. See Section 8.5 for guidance on ION-682884 or inotersen dosing relative to platelet monitoring. After the last dose of inotersen (Week 34), monitoring should be performed every 2 weeks for 8 weeks (until Week 42, inclusive), either by Chemistry, Hematology or Urinalysis panel or by Abbreviated Monitoring panel.

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

a Pre-dose

b 1, 2, 3, 4, 6 hours for PK subgroup only

APPENDIX B. LIST OF LABORATORY ANALYTES

Appendix B List of Laboratory Analytes

Based on emerging data from this or future studies, additional tests not listed below may be performed on stored samples to better characterize the profile of ION-682884 or other similar oligonucleotides.

Chemistry Panel	**Screening Tests**	**Hematology**	**Inflammatory[5]**
Sodium	Hepatitis B surface antigen	Red blood cells	hs-CRP
Potassium	Hepatitis C antibody	Hemoglobin	
Chloride	HIV antibody	Hematocrit	**Urinalysis[5]**
Bicarbonate	FSH (women only)	MCV, MCH, MCHC, RDW, MPV	Color
Total protein	HbA1c	Platelets	Appearance
Albumin	SPEP with immunofixation	White blood cells	Specific gravity
Calcium	UPEP with immunofixation	WBC Differential (% and absolute)	pH
Magnesium	Serum free light chain ratio	Neutrophils	UPCR and UACR
Phosphorus		Eosinophils	Protein
Glucose	**Pregnancy Test[1]**	Basophils	Blood
BUN	Serum βhCG or urine βhCG	Lymphocytes	Ketones
Creatinine		Monocytes	Urobilinogen
eGFR	**Coagulation**		Glucose
Cystatin C	aPTT (sec)	**Thyroid Panel**	Bilirubin
Uric Acid	PT (sec)	TSH	Leukocyte esterase
Total bilirubin	INR	Free T4 (FT4)[4]	Nitrate
Direct (conjugated) bilirubin		Total T3 (TT4)[4]	Microscopic examination[3]
Indirect (unconjugated) bilirubin	**Other[5]**	**Pharmacokinetics[2]**	**Abbreviated Monitoring Panel**
ALT	Serum Tranthyretin	ION-682884 in plasma	Total bilirubin, direct bilirubin, indirect bilirubin, ALT, AST, ALP, BUN, creatinine, eGFR, Cystatin C, UPCR, Platelets
AST	Retinyl Palmitate (fasting)	Inotersen in plasma	
ALP	Serum Vitamin A		
Gama-Glutamyl Transferase	Neurofilament Light Chain	**Immunogenicity**	
Creatine kinase	Neurofilament Heavy Chain	Anti-ION-682884 antibodies	
		Anti-inotersen antibodies	
Immunoglobulins			
Total IgG		**Cardiac Biomarkers**	
Total IgM		NT-proBNP	
		High-sensitivity Troponin T	
		CK-MB	

[1] Conducted only in women who are of child-bearing potential per Inclusion Criterion 3 iv. Pregnancy test should be conducted on serum or plasma samples at Screening and during in-clinic visits. During visits at home, pregnancy test can be conducted on urine or Serum/plasma.

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

[3] Will be performed on abnormal findings unless otherwise specified

[4] To be measured if TSH is outside of normal range

[5] Other biomarkers may be measured, as needed; at the discretion of the Sponsor. Back-up samples will be collected and stored. For transthyretin, back-up samples may be analyzed in more sensitive transthyretin assays at the discretion of the Sponsor. Back-up urine samples may be analyzed for additional renal biomarkers

APPENDIX C. PK SAMPLING SCHEDULE

Appendix C PK Sampling Schedule

All Patients *except* PK Subgroup Patients

W1	**W5**	**W13**	**W25**	**W33**	**W35**	**W49**	**W57**	**W65**	**W66**	**W73**	**W81**	**W85**	**W93**	**W105**
D1	**D29**	**D85**	**D169**	**D225**	**D239**	**D337**	**D393**	**D449**	**D456**	**D505**	**D561**	**D589**	**D645**	**D729**
Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Anytime	Pre-dose	Pre-dose	Pre-dose	Anytime	Pre-dose	Pre-dose	Anytime	Anytime	Anytime

PK Subgroup Only

W1	**W5**	**W13**	**W25**	**W33**	**W35**	**W49**	**W57**	**W65**	**W66**	**W73**	**W81**	**W85**	**W93**	**W105**
D1	**D29**	**D85**	**D169**	**D225**	**D239**	**D337**	**D393**	**D449**	**D456**	**D505**	**D561**	**D589**	**D645**	**D729**
Pre-dose, 1, 2, 3, 4, and 6 hours post-SC injection	Pre-dose	Pre-dose	Pre-dose	Pre-dose, 1, 2, 3, 4, and 6 hours post-SC injection	Anytime	Pre-dose	Pre-dose	Pre-dose, 1, 2, 3, 4, and 6 hours post-SC injection	Anytime	Pre-dose	Pre-dose	Anytime	Anytime	Anytime

SC = subcutaneous D = Day W = Week

APPENDIX D. GRADING SCALE FOR ADVERSE EVENTS RELATING TO LABORATORY ABNORMALITIES

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

The following grading recommendations for adverse events relating to lab test abnormalities and adverse events at the injection site are based upon the CTCAE Version 5.0, November 2017

Adverse Event	Mild	Moderate	Severe
Hematology			
aPTT prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; bleeding
Eosinophils increased'	>ULN and >Baseline	-	Steroids Initiated
Fibrinogen decreased	<1.0 - 0.75 x LLN; if abnormal, <25% decrease from baseline	<0.75 - 0.5 x LLN; if abnormal, 25 - <50% decrease from baseline	<0.5 x LLN; if abnormal, ≥50% decrease from baseline
Hemoglobin decreased (Anemia)	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated
Hemoglobin increased**	Increase in >0 - 2 g/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 g/dL above ULN or above baseline if baseline is above ULN	Increase in >4 g/dL above ULN or above baseline if baseline is above ULN
INR increased	>1.2 - 1.5; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5; >1.5 - 2.5 x baseline if on anticoagulation; monitoring only indicated	>2.5; >2.5 x baseline if on anticoagulation; dose adjustment indicated
Lymphocyte count decreased	<LLN - 800/mm^3; <LLN - 0.8 x 10^9/L	<800 - 500/mm^3; <0.8 - 0.5 x 10^9 /L	<500 /mm^3; <0.5 x 10^9 /L
Lymphocyte count increased	-	>4000/mm^3 - 20,000/mm^3	>20,000/mm^3
Neutrophil count decreased	<LLN - 1500/mm^3; <LLN - 1.5 x 10^9 /L	<1500 - 1000/mm^3; <1.5 - 1.0 x 10^9 /L	<1000/mm^3; <1.0 x 10^9 /L
Platelet count decreased	<LLN - 75,000/mm^3; <LLN - 75.0 x 10^9 /L	<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9 /L	<50,000/mm^3; <50.0 x 10^9 /L
White blood cell decreased	<LLN - 3000/mm^3; <LLN - 3.0 x 10^9 /L	<3000 - 2000/mm^3; <3.0 - 2.0 x 10^9 /L	<2000/mm^3; <2.0 x 10^9 /L
Chemistry			
Acidosis	pH <normal, but >=7.3	-	pH <7.3
Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline normal 1.5 - 3.0 x baseline if baseline abnormal	>3.0 - 5.0 x ULN if baseline normal >3.0 - 5.0 x baseline if baseline abnormal	>5.0 x ULN if baseline normal >5.0 x baseline if baseline abnormal
Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline normal 2.0 - 2.5 x baseline if baseline abnormal	>2.5 - 5.0 x ULN if baseline normal >2.5 - 5.0 x baseline if baseline abnormal	>5.0 x ULN if baseline normal >5.0 x baseline if baseline was abnormal
Alkalosis	pH >normal, but ≤7.5	-	pH >7.5
Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline normal 1.5 - 3.0 x baseline if baseline abnormal	>3.0 - 5.0 x ULN if baseline normal >3.0 - 5.0 x baseline if baseline abnormal	>5.0 x ULN if baseline normal >5.0 x baseline if baseline abnormal
Blood bilirubin increased	>ULN - 1.5 x ULN if baseline normal >1.0 - 1.5 x baseline if baseline abnormal	>1.5 - 3.0 x ULN if baseline normal >1.5 - 3.0 x baseline if baseline abnormal	>3.0 x ULN if baseline normal >3.0 x baseline if baseline abnormal
Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer

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

Adverse Event	Mild	Moderate	Severe
Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer
CD4 lymphocytes decreased	<LLN - 500/mm^3; <LLN - 0.5 x 10^9 /L	<500 - 200/mm^3; <0.5 - 0.2 x 10^9 /L	<200/mm^3; <0.2 x 10^9 /L
CPK increased*	>ULN - <6 ULN	6 - 10 x ULN	>10 x ULN
Creatinine increased**	>ULN - 1.5 x ULN if baseline normal > 1.0 - 1.5 x baseline if baseline abnormal	>1.5 - 3.0 x ULN if baseline normal >1.5 - 3.0 x baseline if baseline abnormal	>3.0 x ULN if baseline normal >3.0 x baseline if baseline abnormal
GGT increased	>ULN - 2.5 x ULN if baseline normal 2.0 - 2.5 x baseline if baseline abnormal	>2.5 - 5.0 x ULN if baseline normal >2.5 - 5.0 x baseline if baseline abnormal	>5.0 x ULN if baseline normal >5.0 x baseline if baseline abnormal
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 mg/dL; >3.1 mmol/L; Ionized calcium >1.6 mmol/L; hospitalization indicated
Hyperglycemia††	Fasting glucose value ≥126 mg/dL (7.0 mmol/L)	Change in daily management to maintain fasting blood glucose <126 mg/dL (7.0 mmol/L); e.g. addition of oral antiglycemic agent; workup for diabetes	Insulin therapy initiated; hospitalization indicated
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L; intervention initiated	>6.0; hospitalization indicated
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 mg/dL; >1.23 mmol/L
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L; intervention initiated	>155 mmol/L; hospitalization indicated
Hyperphosphatemia	Laboratory finding only and intervention not indicated	Noninvasive intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated
Hyperuricemia	>ULN without physiologic consequences	-	>ULN with physiologic consequences
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 mg/dL; <1.75 mmol/L; Ionized calcium <0.9 mmol/L; hospitalization indicated
Hypoglycemia‡	≥54 mg/dL - <70 mg/dL ≥3.0 mmol/L - <3.9 mmol/L	<54 mg/dL (3.0 mmol/L) AND no assistance required to actively administer carbohydrates, glucagon, or take other corrective actions	Requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions
Hypokalemia	<LLN - 3.0 mmol/L	symptomatic with <LLN - 3.0 mmol/L; intervention indicated	<3.0 mmol/L; hospitalization indicated
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 mg/dL; <0.4 mmol/L
Hyponatremia	<LLN - 130 mmol/L	125-129 mmol/L and asymptomatic	125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms
Hypophosphatemia	Laboratory finding only and intervention not indicated	Oral replacement therapy indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 x ULN with signs or symptoms
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 x ULN with signs or symptoms

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

Adverse Event	Mild	Moderate	Severe
Urine			
Proteinuria Adults	1+ proteinuria; urinary protein ≥ULN - <1.0 g/24 hrs	2+ and 3+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs;	4+ proteinuria; Urinary protein ≥3.5 g/24 hrs;
Children	-	Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Urine P/C >1.9
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective invasive intervention indicated
Adverse Events at the Injection Site			
Adverse events at the injection site**	An event at the injection site (e.g. erythema, tenderness, itching) that is easily tolerated by the subject and does not affect the subject's usual daily activities	- Persistent (>24 hours) pain, phlebitis or edema; OR - Lipodystrophy, hair growth or alopecia, OR - Prolonged (>1 month) hypo/hyperpigmentation	- Ulceration or necrosis; severe tissue damage; operative intervention indicated, OR - Any event at the injection site that is incapacitating

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

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

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

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

**Adapted from the original CTCAE V5.0 scale

PAREXEL International

IONIS PHARMACEUTICALS, INC.

ION-682884-CS3

A Phase 3 Global, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of ION-682884 in Patients with Hereditary Transthyretin-Mediated Amyloid Polyneuropathy

Statistical Analysis Plan

Final Version: 2.1

[redacted]

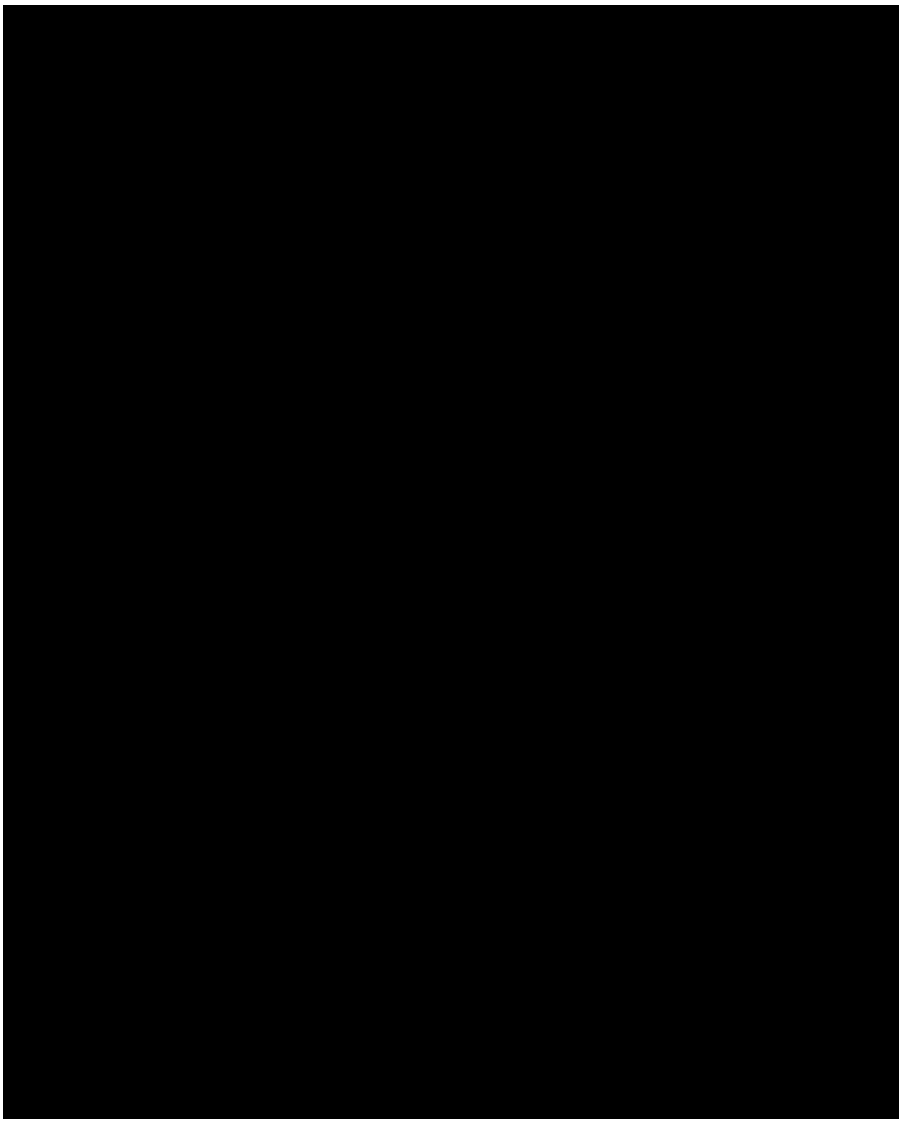
PAREXEL International

IONIS PHARMACEUTICALS, INC.

ION-682884-CS3 Statistical Analysis Plan

SPONSOR SIGNATURE PAGE

Approved by:



PAREXEL SIGNATURE PAGE

Signature(s) below confirm that the Statistical Analysis Plan was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

	[redacted]
Author	

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition / Expansion
10MWT	10-meter walk test
ADA	Anti-drug antibody
ADaM	Analysis Data Model
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
BMI	Body mass index
BP	Bodily pain
C_{max}	Maximum observed plasma concentration; obtained directly from the plasma concentration-time profile
CI	Confidence interval
CICL	Cardiac Imaging Core Laboratory
CIR	Copy Increment from Reference
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CNS	Central Nervous System
COMPASS-31	Composite Autonomic Symptom Score-31
CRF	Case report form
CRNMB	Clinically relevant, non-major bleeding
CRO	Contract research organization
DIC	Disseminated intravascular coagulation
DSMB	Data and safety monitoring board
ECG	Electrocardiogram
ECHO	Echocardiogram
ECL	Electrochemiluminescence
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EOS	End of study
EOT	End of treatment
EQ-5D-5L	5-level EQ-5D version
FAC	Familial amyloid cardiomyopathy
FAP	Familial amyloid polyneuropathy
FAS	Full Analysis Set
GH	General health

GLS	Global longitudinal strain
hATTR-PN	Hereditary transthyretin-mediated amyloid polyneuropathy
HLT	Higher level term
HP	Heat pain
HRDB	Heart Rate to Deep Breathing
IEC	Independent ethics committee
IM	Immunogenicity
INR	International normalized ratio
IRB	Institutional review board
IVS	Intraventricular septum
J2R	Jump to reference
LCRIS	Local cutaneous reactions at injection site
LLOQ	Lower limit of quantification
LV	Left ventricular
MAR	Missing at Random
MB	Major bleeding
mBMI	Modified body mass index
MC Core	Mayo Clinic Polyneuropathy Quality Assurance Core Facility
MCS	Mental component summary
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mental Health
MMRM	Mixed effects model with repeated measures
mNIS+7	Modified neuropathy impairment Score +7. Standard NIS+7 but with modifications made to the +7 component
Modified +7	+7 test with modifications made to the sensory and nerve conduction testing
NCT	Nerve Conduction Test
NEURO-TTR	ISIS 420915-CS2
NIS	Neuropathy impairment score
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	Neuropathy symptoms and change
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
OLE	Open-label extension
P25	25th percentile
P75	75th percentile
PCS	Physical component summary
PD	Pharmacodynamic
PF	Physical functioning
PGIC	Patient Global Impression of Change

PGIS	Patient Global Impression of Severity
PK	Pharmacokinetic
PMAK	Fibular CMAP amplitude
PMCVK	Fibular nerve motor conduction velocity
PMLA	Fibular nerve distal latency
PND	Polyneuropathy disability
PPS	Per Protocol Set
PT	Preferred term
QTc	QT interval corrected for heart rate
QTcB	QTc interval calculated using Bazett's formula
QTcF	QTc interval calculated using Fridericia's formula
RE	Role-Emotional
R-ODS	Rasch-built Overall Disability Score
RP	Role-Physical
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SDTM	Study Data Tabulation Model
SE	Standard error
SF	Social Functioning
SF-36	Short Form (36) Health Survey
SMQ	Standardized MedDRA query
SOC	System Organ Class
SS	Safety set
SSAB	Sural SNAP amplitude
Study Day 1	Defined as the first day Study Drug is administered to the patient
Study Drug	ION-682884 or inotersen
TEAE	Treatment emergent adverse event
t_{max}	Time to reach C_{max}; obtained directly from the plasma concentration-time profile
TMLA	Tibial nerve distal latency
TP	Touch pressure
TTP	Thrombotic thrombocytopic purpura
TTR	Transthyretin
ULN	Upper limit of normal
UPCR	Urine protein/creatinine ratio
VAS	Visual analog scale
VT	Vitality
WHO-DD	World Health Organization-Drug Dictionary

1 INTRODUCTION

This Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing study data and outlines the statistical programming specifications for the Tables, Listings and Figures. It describes the variables and populations, anticipated data transformations and manipulations and other details of the analyses not provided in the Clinical Study Protocol.

The analyses described in this SAP are based upon the following study documents:

- Amendment 4 - Japan 20-Nov-20
- Amendment 5 - Canada 19-Aug-21
- Amendment 5 - Turkey 27-Aug-21
- Amendment 5 – ROW 12-Aug-21
- Amendment 6 - USA Only 18-Aug-21
- Amendment 6 - Sweden 23-Aug-21
- Amendment 6 - Germany 28-Sep-21
- Amendment 6 – Spain 26-Aug-21
- Amendment 7 - France 18-Aug-21
- Electronic Case Report Form (eCRF), Version 8.0 (December 22, 2021)

Section 2 indicates the study objectives. Section 3 provides overall study design and study endpoints. Section 4 presents statistical methods, including general guidelines to be followed for all analyses, the analysis population, handling of missing data, definition of Baseline and visit window, discussion for the primary/secondary efficacy and the sensitivity analyses, and details for pharmacodynamic (PD) endpoints and pharmacokinetic (PK) analyses.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to evaluate the efficacy of ION-682884 after administration for 65 weeks, as compared to the historical control of the placebo cohort in the ISIS 420915-CS2 (NEURO-TTR) trial, based on the change from Baseline in serum transthyretin (TTR) concentration, modified Neuropathy Impairment Score +7 (mNIS+7), and in the Norfolk Quality of Life Questionnaire—Diabetic Neuropathy (Norfolk QOL-DN) in patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy (hATTR-PN).

An interim analysis will be conducted at Week 35. The interim analysis will be performed when all patients on ION-682884 complete Week 35 assessments, and will assess the efficacy (TTR, mNIS+7, Norfolk) compared to the placebo arm of the NEURO-TTR trial.

2.2 Secondary Objectives

To evaluate the efficacy of ION-682884, as compared to the placebo cohort in the NEURO-TTR trial, based on the change from Baseline in the following measures:

- Neuropathy Symptom and Change (NSC) score
- Physical component summary (PCS) score of 36-Item Short Form Survey (SF-36)
- Polyneuropathy disability (PND) score
- Modified body mass index (mBMI)

2.3 Safety Objectives

To evaluate safety and tolerability in hATTR-PN patients treated with ION-682884, including the change from Baseline in platelet count and renal function and the presence of adverse events (AEs).

2.4 Additional/Exploratory Objectives

2.4.1 Efficacy Objectives

To evaluate the efficacy of ION-682884 in mNIS+7 at Week 85, compared to Baseline.

To evaluate the efficacy of ION-682884 in the change from Baseline in the Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) at Weeks 37 and 85.

To evaluate the efficacy of ION-682884, as compared to the historical control of the placebo arm included in the ALN-TTR02-004 (APOLLO trial, ClinicalTrials.gov Identifier: NCT01960348), in the following measures:

- Change from Baseline in Norfolk QOL-DN at Week 85
- Change from Baseline in 10-Meter Walk Test (10MWT) at Weeks 37 and 81
- Change from Baseline in Rasch-built Overall Disability Score (R-ODS) at Weeks 37 and 81
- Change from Baseline in Composite Autonomic Symptom Score-31 (COMPASS-31) at Weeks 37 and 81
- Change from Baseline in 5-level EQ-5D version (EQ-5D-5L) at Weeks 37 and 81

To evaluate the efficacy of ION-682884, as compared to the placebo cohort of the NEURO-TTR trial, in:

- Change from Baseline in the SF-36 at Weeks 35
- Frequency of all-cause hospitalizations (in all patients and in patients with cardiac involvement) by Week 66
- Change from Baseline in transthoracic echocardiogram (ECHO) parameters, including left ventricular (LV) mass, LV wall thickness, intraventricular septum (IVS) thickness, and global longitudinal strain (GLS), in patients with cardiac involvement at Weeks 65.
- Change from Baseline in N-terminal pro b-type natriuretic peptide (NT-proBNP) in patients with cardiac involvement at Weeks 65.
- Change from Baseline in PGIS and PGIC at Week 37 and 85

2.5 PK Objectives

To evaluate the plasma trough and post-treatment concentrations of ION-682884 or inotersen in all patients, and to evaluate plasma PK parameters in a subset of patients.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a Phase 3 multicenter, open-label, randomized study of ION-682884 in Stage 1 and Stage 2 hATTR-PN patients with a Neuropathy Impairment Score (NIS) of 10 to 130, with a concurrent reference arm of inotersen. Approximately 140 patients will be randomized 6:1 (ION-682884: inotersen) to receive [redacted] ION-682884 subcutaneous (SC) injection once every 4 weeks [redacted] or inotersen [redacted] SC once every week [redacted] Patients enrolled in the ION-682884 arm will be compared to patients enrolled in the placebo cohort group in the NEURO-TTR trial.

An interim analysis will be conducted at Week 35, with primary efficacy analysis at Week 66. The interim analysis will be performed when all patients on ION-682884 complete Week 35 assessments, and will assess the efficacy (TTR, mNIS+7, Norfolk) compared to the placebo arm of the NEURO-TTR study and safety of ION-682884 compared to the inotersen and placebo arm of the NEURO-TTR study and inotersen reference arm in 682884-CS3.

Patients in the reference arm (inotersen) will be crossed over to ION-682884 once they complete Week 35 assessments. These patients will start ION-682884 at Week 37. All patients will continue dosing with ION-682884 until Week 81 with end-of-treatment (EOT) assessments at Week 85, 4 weeks after the last dose.

Approximately 28 patients at selected sites (~22 receiving ION-682884 and ~6 receiving inotersen) will be enrolled in a PK subgroup and will receive additional sampling for PK.

Following treatment and the EOT assessments, eligible patients may elect to enroll in an open-label extension (OLE) study, pending study approval by the institutional review board (IRB)/ independent ethics committee (IEC) and the appropriate regulatory authorities. All participating patients in the OLE study will continue to receive ION-682884 once every 4 weeks.

Patients not participating in the OLE will enter the 20-week post-treatment evaluation portion of this study after completing the EOT assessments.

3.2 Study Endpoints

3.2.1 Interim Analysis Co-Primary Efficacy Endpoints at Week 35

- Percent change from Baseline in serum TTR concentration at Week 35
- Change from Baseline in mNIS+7 at Week 35

3.2.2 Interim Analysis Key Secondary Efficacy Endpoint at Week 35

- Change from Baseline in Norfolk QOL-DN at Week 35

3.2.3 Final Analysis Co-Primary Efficacy Endpoints

- Percent change from Baseline in serum TTR concentration at Week 65

- Change from Baseline in mNIS+7 at Week 66
- Change from Baseline in Norfolk QOL-DN at Week 66
  In the Week 66 Final Analysis, for those statistically significant endpoints at the Week 35 interim analysis, their corresponding tests at the Week 66 final analysis will not be conducted (See Section 4.10.2.3).

3.2.4 Final Analysis Secondary Endpoints

- Change from Baseline in NSC at Weeks 66
- Change from Baseline in NSC at Weeks 35
- Change from Baseline in the PCS score of SF-36 at Week 65
- Change from Baseline in PND score at Week 65
- Change from Baseline in mBMI at Week 65

3.2.5 Safety Endpoints

- Change from Baseline in platelet count during the Treatment Period
- Change from Baseline in renal function during the Treatment Period
- Adverse events
- Vital signs and weight
- Physical examination
- Clinical laboratory tests
- Electrocardiogram (ECG)
- Use of concomitant medication
- Ophthalmology examination
- Thyroid panel
- Inflammatory panel
- Coagulation
- Immunogenicity

3.2.6 Additional/Exploratory Endpoints

3.2.6.1 Efficacy Endpoints

- Change from Baseline in mNIS+7 at Week 85
- Change from Baseline in Norfolk QOL-DN at Week 85
- Change from Baseline in 10MWT at Weeks 37 and 81
- Change from Baseline in R-ODS at Weeks 37 and 81
- Change from Baseline in COMPASS-31 at Weeks 37 and 81
- Change from Baseline in EQ-5D-5L at Weeks 37 and 81
- Change from Baseline in the SF-36 components at Weeks 35
- Frequency of all cause hospitalizations in all patients and in patients with cardiac involvement by Week 66
- Change from Baseline in transthoracic ECHO parameters, including LV mass, LV wall thickness, IVS thickness, and GLS, in patients with cardiac involvement at Week 65
- Change from Baseline in NT-proBNP in patients with cardiac involvement at Week 65
- Change from Baseline in PGIS at Week 37 and 85

- Change from Baseline in PGIC at Week 37 and 85

3.2.6.2 Pharmacokinetic Endpoints

Plasma trough and post-treatment concentrations of ION-682884 or inotersen in all patients; area under the curve (AUC), maximum observed plasma concentration (C_{max}), and time to reach C_{max} (t_{max}) obtained directly from the plasma concentration-time profile in a subset of patients (PK subgroup); and $t_{½\lambda z}$ for patients who do not roll over to the OLE study.

3.3 Trial Design Considerations

3.3.1 Background

ION-682884 is a ligand-conjugated antisense oligonucleotide (LICA), specifically a second-generation 2′-MOE of twenty (20) nucleotides (i.e., a 20-mer) that are connected sequentially by phosphorothioate and phosphate diester internucleotide linkages and conjugated at the 5′ end to a triantennary *N*-acetyl galactosamine (GalNAc) moiety. GalNAc conjugation enhances the uptake of ASOs to hepatocytes, and thereby increases the potency of ASOs in humans up to approximately 30-fold. The strategy for treatment of transthyretin-mediated amyloidosis (ATTR) with systemically delivered ION-682884 is to reduce levels of mutated and wild-type TTR protein secreted by the liver. This strategy has been validated by the successful Phase 2/3 NEURO-TTR study of Tegsedi (inotersen), an unconjugated 2′-MOE PS ASO which shares ION-682884's nucleotide sequence, which demonstrated improvement in the course of neurologic disease and quality of life in patients with stage 1 and stage 2 hereditary ATTR with polyneuropathy (hATTR-PN).

Currently, two products are approved globally for the treatment of hATTR-PN: Tegsedi (inotersen), and Onpattro (patisiran), an RNAi product which also reduces levels of TTR protein, and which is administered intravenously. A third product, Vyndaqel (tafamidis), a tetrameric TTR stabilizer, is approved in some countries for treatment of symptomatic stage 1 hATTR-PN patients. Treatment with inotersen is associated with risks of severe thrombocytopenia and glomerulonephritis.

In light of hATTR's status as a rare disease, as well as the current highly competitive environment for recruitment of hATTR patients, the sponsor's objective is to conduct a pivotal registration study which represents a scientifically valid assessment of ION-682884's clinical efficacy in treatment of hATTR-PN, while also being sufficiently appealing to patients to both accrue the study within a reasonable time frame and retain all subjects throughout the treatment period. The concurrent reference cohort of patients receiving open-label inotersen in ION-682884-CS3 will be descriptively compared to the historical inotersen cohort of NEURO-TTR to validate efficacy comparisons between the two studies.

3.3.2 Risks of bias and mitigation of bias

Externally controlled studies face important risks of bias. The design of the present study aims to mitigate these risks as follows, considering the framework provided by Pocock 1976 and E10 guidance:

This trial is a randomized open-label study that compares the active ION-682884 arm to historical control data from another trial. This design has several limitations compared to a double-blind, randomized, placebo-controlled trial. An open-label trial is subject to more bias when compared to a blinded trial, and data from two trials performed at different times leads to questions of the validity of such a comparison. The sponsor acknowledges these limitations, but believes this is a unique situation in which comparison to historical control is justified.

Firstly, the historical control data were collected in a randomized, double-blinded, placebo-controlled trial (NEURO-TTR) in the same disease population within the last 8 years by the same sponsor. The trial was accepted by multiple regulatory agencies and supported the approval of the drug inotersen. Secondly, as the study is being supported by many of the same sites and original study team members, similar mitigations and trial conduct will be employed in the current study. Finally, several measures have been instituted in the current trial to ensure the integrity of the trial conduct and validity of data comparison. They are listed below:

Patient population:

- Eligibility criteria are designed to mirror those in NEURO-TTR in defining hATTR-PN disease stage, age range, gender, exclusions of certain comorbidities, restriction of concomitant medications for hATTR and functional status.

Sites and regions:

- Sites that participated in NEURO-TTR are also participating in the current trial. Additional sites and regions have been added to enhance enrollment; however, all of the selected sites have experience with hATTR disease management. Since this is a rare disease, participating clinicians are generally active in international congresses in which practice guidance and experiences are exchanged and aligned.
- Oversight of sites by the study team, especially the new sites not involved in NEURO-TTR, will ensure that the trial conduct is as similar as possible to NEURO-TTR.

Primary endpoint evaluation comparison.

The primary endpoint evaluation is consistent between the NEURO-TTR and ION-682884-CS3 studies. Measures have been taken to maximize the validity of the comparison. The primary endpoints of mNIS+7 and Norfolk QOL-DN will be masked to the sponsor team responsible for oversight of the study. Any team members that become unblinded at the time of interim analysis will be replaced with blinded team members. Further details are described in the Unblinding and Data Access Plan. Similarly to NEURO-TTR, the mNIS+7 central reader at PNRL, Mayo Clinic, will be blinded to treatment assignment. All mNIS+7 assessors will be blinded to the rest of trial conduct. For mNIS+7 evaluation, the conduct of the primary endpoint assessment is similar to NEURO-TTR, i.e., mNIS+7 assessors will be trained and certified by Dr. Peter Dyck, a neurologist at PNRL, Mayo Clinic, who created the composite score. Dr. Dyck's team will be the central reader to review and normalize the results. Pharmacodynamic markers will be blinded to sites and patients.

Open-label bias for endpoints. Patient- or clinician-reported outcomes may incur response bias in open-label designs. To assess this risk for key outcome measures, we visually inspected the effect of inotersen on changes in mNIS+7 and Norfolk QoL during the double-blind period in NEURO-TTR, and crossover from placebo to open-label inotersen in the NEURO-TTR OLE study (see figures below). Open-label bias was not visually evident based on the fact that the slope of disease progression is similar before and after the change to open label. Furthermore, although participants are not blinded to treatment assignment, the primary outcome assessments of serum TTR reduction and mNIS+7 scores are largely objective, and no formal statistical comparison will be made between the reference inotersen arm and the ION-682884-treated arm.

[redacted]

[redacted]

Safety monitoring comparison. The important identified risks of Tegsedi (inotersen) are thrombocytopenia and glomerulonephritis, and are monitored by laboratory values (platelet and renal parameters), which are objective. The safety monitoring rules for ION-682884-CS3 are mostly similar to NEURO-TTR and will allow clinically relevant cases to be monitored by the study team to ensure safety and consistency. AEs related to flu-like reactions and injection site

reactions will be analyzed by definitions that are designed to identify clinically relevant cases and are defined identically between NEURO-TTR and ION-682884-CS3. The Adverse Events of Special Interest (AESI) and Other Adverse Events of Interest (OAEI) are the same between NEURO-TTR and ION-682884-CS3, with the exception that a renal impairment AESI has been moved to OAEI and replaced with glomerulonephritis AESI, a cardiac OAEI has been added. The complement activation was removed because using the hypersensitivity SMQ was not very specific to compliment activation and in NEURO-TTR did not show any differences from placebo. The Cardiac OAEI uses standard MedDRA terms so can be applied to both the ION-682844 and comparator arms consistently

Baseline factor adjustment. The following baseline factors will be used in the propensity score for baseline factor adjustment based on the NEURO-TTR analysis: disease stage, previous treatment, and V30M mutation. In addition to the three factors used in the primary analyses, some sensitivity analyses may include the following factors in the logistic model for the propensity score.

- Gender (Male, Female)
- Modified BMI baseline (continuous value)
- Region (Europe, North America, South America/Australasia/Asia)

For the MMRM and ANCOVA analyses, baseline result of the endpoint will be used as the covariate, if applicable.

4 STATISTICAL METHODS

4.1 Data Management and Quality Assurance

ICON plc (nee PRA) has been contracted to provide Data Management services for this study. As part of the contract, ICON (nee PRA) is responsible for creating the Medidata RAVE Electronic Data Capture (EDC) data entry screens, database and edit checks using definitions developed together with Ionis Pharmaceuticals, Inc. In addition to database development, ICON (nee PRA) is also responsible for the clinical database maintenance throughout the course of the study (i.e., amendments), as well as 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 at the time of data entry within EDC, and automatic queries are generated. ICON (nee PRA) reviews all data for accuracy and validity and generates additional manual queries in the EDC system when necessary. The data are corrected, or an explanation concerning the query is provided in the EDC system and saved in the audit trail.

Exceptions for data entry are protocol deviations entered by the ICON (nee PRA) monitors, and mNIS+7 data, which are entered into the EDC by an independent contract research group, the Mayo Clinic Polyneuropathy Quality Assurance Core Facility (MC Core), which is under the direction of Dr. Peter Dyck. These mNIS+7 eCRFs are restricted from review by both ICON (nee PRA) and Ionis Pharmaceuticals, Inc. (Note that the CNA Booklet data at the Screening Visit is available for review by both ICON (nee PRA) and Ionis Pharmaceuticals, Inc.).

For the purpose of data cleaning, a firewalled data manager at the CRO contracted to perform data management (TRENNIC Data Services) will have access to the post-baseline mNIS+7, NSC, Norfolk-QOL-DN. This data manager will not communicate or discuss the firewalled data with the rest of Ionis team.

After all data are entered, reviewed, and queried, the database is closed and sent to the statistics group for review and for identification of significant protocol deviations. After any further queries that arose from this review are resolved, the database is locked. Database interim locks will be done at Week 35, Week 66, and after all patients have completed the EOT assessments. The final data base lock will be performed after all subjects complete the study, and is referred to as the end of study (EOS) final lock. Further details can be found in the Data Management Plan.

4.1.1 Laboratory Data

Ionis Pharmaceuticals, Inc. and ICON (nee PRA) are responsible for the format of the laboratory electronic data transfers and the transfer schedule. Central laboratory, MedPace, data results are not stored in the EDC system. ICON (nee PRA) and Ionis Pharmaceuticals, Inc. are responsible for the review of the clinical laboratory data. This process involves reviewing the patient and visit identifiers in the central laboratory data results data against the central lab data identifiers collected 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). Local laboratory results, if any, will be entered directly in EDC by site staff; monitors will review against laboratory reports and local laboratory normal reference ranges document, and ICON (nee PRA) data management team will perform standard data review of local laboratory results as well.

4.1.2 Biomarker Data

Immunologix Laboratories is contracted and responsible for analyzing Transthyretin (TTR), Neurofilament Light Chain (NfL) and Neurofilament Heavy Chain (NfH). Ionis Pharmaceuticals, Inc. is responsible for the format of the electronic data transfers and the transfer schedule. Ionis Pharmaceuticals, Inc. and ICON (nee PRA) are responsible for the data reconciliation of the results data. This process involves reviewing the patient and visit identifiers in the lab results data against the lab data collected in the EDC system.

4.1.3 PK Data

Ionis Pharmaceuticals, Inc. is responsible for the management and review of the PK data. This process involves reviewing the patient and visit identifiers with the clinical data collected in the EDC system. The PK data are not stored in the EDC system.

4.1.4 Echocardiogram (ECHO) Data

The Echocardiogram (ECHO) data will be collected, analyzed, and stored in a secure database by an independent Contract research organization (CRO) (Cardiac Imaging Core Laboratory and Clinical Trials Endpoints Center at the Brigham and Women's Hospital [CICL]). The sites will upload the echocardiogram (ECHO) data on a secure web-portal for analysis by CICL. CICL will only inform the site whether the echo images are of acceptable quality or not. CICL will not provide a formal report, read, or clinical data to the sites. Echocardiogram (ECHO) results data are not

stored in the EDC system. Ionis Pharmaceuticals, Inc. and ICON (nee PRA) are responsible for the format of the echocardiographic electronic data transfers and the transfer schedule. Ionis Pharmaceuticals, Inc., and ICON (nee PRA) are responsible for the data reconciliation of the echocardiogram (ECHO) results data. This process involves reviewing the patient and visit identifiers in the echocardiogram (ECHO) results data against the echocardiogram (ECHO) data collected in the EDC system.

4.1.5 ECG Data

All ECG data (machine read after review by PI) are entered into the Medidata Rave EDC by the sites. The Rave EDC data will be used for ECG summary and analysis.

4.1.6 mNIS+7, NSC Score, and Norfolk

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), which is under the direction of Dr. Peter Dyck. 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 transmitted via EDC to MC Core for processing and quality assurance. The mNIS+7 data are retained and stored in EDC. All of the mNIS+7 data are entered by the MC Core into a restricted portion of the study EDC system. Only MC Core and the pre-identified Ionis data manager have unrestricted access to this portion of the EDC system. 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 until after the study is completed. Up until Week 35 interim analysis, the Sponsor will only have access to patient screening Total NIS Score and baseline visit data.

The primary endpoints of mNIS+7 and Norfolk QOL-DN will be masked to the sponsor team responsible for oversight of the study and any team members that become unblinded at the time of interim analysis will be replaced with blinded team members.

4.1.7 SF-36 Data and Scoring

The 36-Item Short Form Survey (SF-36) will be entered in EDC by site staff, and monitored and data reviewed by ICON (nee PRA). Ionis Pharmaceuticals, Inc. data management is responsible for scoring the raw data entered in EDC using the Quality Metric PRO CoRE Smart Measurement System, PRO CoRE Version 2.1 software, and providing SF-36v2® Health Survey scored dataset to the statistics group for analysis.

4.1.8 Medical Coding Data

ICON (nee PRA) is responsible for coding Medical History entries, Adverse Events, as well as Concomitant Medications entered in EDC by site staff, using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary Version 25.0 or later version and WHODRUG Global B3 Mar2022 or later version, respectively. Data management will provide coded datasets to the statistics group for analysis.

4.2 General Presentation Considerations

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

Continuous data will be summarized in terms of the mean, standard deviation (SD), standard error (SE), median, interquartile range (25th percentile [P25], 75th percentile [P75]), range (minimum, maximum) and number of observations, unless otherwise stated. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile, upper quartile, least squares means and difference in least squares means will be reported to one more decimal place than the raw data recorded in the database. The SD and SE will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic. All raw values presented in listings will be displayed to the measured precision.

Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages. Any planned collapsing of categories will be detailed in the text and the data displays.

Age will be presented in years. Weight will be presented in kg. Height will be presented in cm. Temperature will be presented in °C. Laboratory values will be summarized using standard units.

Percentages will be presented to one decimal place and not be presented for zero counts. Percentages will be calculated using n as the denominator.

Changes from Baseline in categorical data will be summarized using shift tables where appropriate.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as "<0.001". All statistical tests will be conducted using 2-sided tests with 5% Type I error rates, unless otherwise stated.

Confidence intervals will be presented to one more decimal place than the raw data.

Summaries of plasma drug concentrations and pharmacokinetic parameters will include typical descriptive statistics, such as n, mean, SD, SE, percent Coefficient of Variation (%CV), geometric mean, geometric %CV, median, minimum, and maximum.

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.

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

The reference arm (inotersen) will be summarized descriptively with the NEURO-TTR inotersen arm. No formal statistical comparison will be made between the reference arm and the ION-682884-treated arm.

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

All tables and figures containing efficacy and PD endpoints will indicate whether they present raw data or adjusted results from the statistical model, with footnotes indicating the model used and covariates included in the model.

All tables, figures, and data listings to be included in the report will be independently checked for consistency, integrity, and in accordance with standard PAREXEL procedures.

All the missing visit or missing data related to COVID-19 will be listed. Additional listings will be provided for the patients' assessments with COVID-19 impact. Additional summary will be provided if deemed necessary.

4.2.1 Baseline

4.2.1.1 Baseline for ION-682884 and inotersen

The same Baseline definitions as in the NEURO-TTR trial will be applied in this study. The Baseline for efficacy, PD, and safety assessments will be defined as follows:

- Baseline mNIS+7 and its individual components will be defined as the average of 2 assessments taken within 60 days prior to the first dose of ION-682884 or inotersen. If only one assessment has been done, the single assessment will be used in place of the average. Rarely, for patient convenience, the Baseline mNIS+7 assessment(s) (or a subset of this assessment) will have been completed early in the Treatment Period rather than pre-treatment. These will be considered protocol deviations. These assessments will be included in the analysis as valid Baseline assessments, provided they are taken within 1 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 primary analysis.
- Baseline NSC and individual components will be defined as the average of 2 assessments taken within 60 days prior to the first dose of ION-682884 or inotersen. If only 1 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, it is possible it could be completed early in the Treatment Period rather than pre-treatment. These will be considered protocol deviations. These assessments will be included in the analysis as valid Baseline assessments provided they are taken within 1 week after the first dose.
- Baseline ECG will be defined as the value taken on Day 1 pre-dose. If the triplicates are taken, the average of the triplicates will be used. If only 1 or 2 assessments are available, the single assessment or average of the 2 assessments will be used. If the case that Day 1 pre-dose ECG is missing, screening visit results will be used as Baseline.
- Baseline for numerical laboratory assessment including PD will be defined as the average of all non-missing pre-dose assessments.

Baseline for all other assessments will be defined as the last non-missing value prior to the first dose of study drug (ION-682884 or inotersen).

Of note, for re-consented and re-screened patients, only records after re-screening will be used for Baseline.

4.2.1.2 ION-682884 Baseline for patients received inotersen at the beginning of study and scheduled to switch to ION-682884 at Week 37

ION-682884 baseline will be defined as the last non-missing assessment prior to the first dose of ION-682884.

4.2.2 Definitions and Computational Formulas

The same on-treatment period definitions as in the NEURO-TTR trial for efficacy and PD data will be applied in this study.

- Day 1 will refer to the day of the first dose of study drug.
- For efficacy endpoints except for BMI and mBMI:
  - The efficacy on-treatment period spans the time during which the study treatment is administered until 52 days after the last dose of medication.
  - The efficacy post-treatment period starts on the day after the efficacy on-treatment period and ends on the day of the patient's last contact date within the study.
- For BMI, mBMI, and PD endpoints:
  - The on-treatment period spans the time during which the study treatment is administered until 28 days after the last dose of medication.
  - The 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.
- For safety endpoints, the safety period spans the time drug is first administered until the day of the patient's last contact date within the study.
- The PK and Immunogenicity (IM) on-study period spans the time drug is administered until the day of the patient's last contact date within the study.
- Note: Assessments for mNIS+7, and NSC done early in the treatment period that are used for baseline cannot also be used as an on-treatment assessment.
- Body mass index (BMI) will be computed using the formula:

  BMI = (weight in kilograms) / [height in cm / 100]^2
- mBMI will be computed from BMI and serum albumin levels by:

  mBMI = BMI * serum albumin (g/L).

4.2.3 Analysis Visit Windows

For 682884-CS3 study, the efficacy and PD data will be assigned to a visit according to the visit windows in the table below. Efficacy assessments that occurred more than 52 days after the last dose of study drug will not be included in the efficacy analyses/summaries during the efficacy on-treatment period, even if they occur within one of the visit windows. PD assessments, as well as

body weight, BMI, and mm, that occurred more than 28 days after the last dose of study drug 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 the study, the visits from the post-treatment evaluation period will not be used. For mNIS+7, the assignment of assessments to a visit is done subcomponent by subcomponent, according to the date the component was assessed. As long as the component is completed within the analysis window and within 52 days of last dose, it is eligible to be used for the efficacy analyses/summaries during the efficacy on-treatment period. If, after subcomponents have been assigned to visit windows, there are two or more subcomponents of the same type within a window, the subcomponent that was assessed closer to the target day (unless it falls in the post treatment period) will be used (or the average of the two, if they are equally close). For baseline and Week 66, the two assessments are averaged (provided both assessments are within the visit window and are within 52 days of the last dose of medication). In case of averaged subcomponents, for the purpose of determining proximity to the visit window target day, the date of the second assessment will be used.

For NEURO-TTR study, nominal visit and target day are different from 682884-CS3. To align with 682884-CS3 visit, the measurement results will be captured from nearest visit corresponding to 682884-CS3 nominal visit.

Efficacy/PD measure	**Nominal Visit (Target Day) in NEURO-TTR**	**Analysis Visit Window (Day) in NEURO-TTR**	**Nominal Visit (Target Day) in 682884-CS3**	**Analysis Visit Window (Day) in 682884-CS3**
mNIS+7 and individual components, NSC, Norfolk QOL-DN and individual components	Week 35 (Day 239)	209-269	Week 35 (Day 239)	209-269
	Week 66 (Day 456)	411-501	Week 66 (Day 456)	411-501
	Week 91 (Day 631)	601-661	Week 85 (Day 589)	544-633
SF-36 Questionnaire, PND Score	Week 35 (Day 240)	210-270	Week 35 (Day 239)	209-269
	Week 65 (Day 449)	419-479	Week 65 (Day 449)	419-479
	Week 91 (Day 631)	559-661	Week 85 (Day 589)	559-619
10MWT, R-ODS, COMPASS-31, EQ-5D-5L			Week 37 (Day 253)	223-283
			Week 81 (Day 561)	531-591
PGIC, PGIS			Week 37 (Day 253)	223-283
			Week 85 (day 589)	559-619
BMI and mBMI	Week 13 (Day 85)	55-115	Week 13 (Day 85)	55-115
	Week 35 (Day 240)	210-270	Week 35 (Day 239)	209-270
	Week 65 (Day 449)	419-449	Week 65 (Day 449)	419-479
	Week 91 (Day 631)	559-661	Week 85 (Day 589)	559-619
Serum TTR and Immunoglobulins (named PD Panel in NEURO-TTR)	Week 5 (Day 29)	22-38	Week 5 (Day 29)	14-42
	Week 8 (Day 50)	39-66	Week 9 (Day 57)	43-70
	Week 13 (Day 85)	67-101	Week 13 (Day 85)	71-126

Efficacy/PD measure	Nominal Visit (Target Day) in NEURO-TTR	Analysis Visit Window (Day) in NEURO-TTR	Nominal Visit (Target Day) in 682884-CS3	Analysis Visit Window (Day) in 682884-CS3
	Week 23 (Day 155)	137-175	Week 25 (Day 169)	127-203
	Week 35 (Day 240)	204-287	Week 35 (Day 239)	204-287
	Week 47 (Day 323)	302-343	Week 49 (Day 337)	288-364
	Week 59 (Day 407)	386-427	Week 57 (Day 393)	365-420
	Week 65 (Day 449)	428-469	Week 65 (Day 449)	421-476
	Week 71 (Day 491)	470-511	Week 73 (Day 505)	477-532
	Week 77 (Day 533)	512-581	Week 81 (Day 561)	533-574
	Week 91 (Day 631)	582-651	Week 85 (Day 589)	575-602
NT-proBNP and Troponin T	Week 13 (Day 85)	55-115	Week 13 (Day 85)	55-115
	Week 35 (Day 240)	210-270	Week 35 (Day 239)	209-269
	Week 65 (Day 449)	397-501	Week 65 (Day 449)	319-479
Transthoracic Echocardiogram (ECHO)	Week 41 (Day 281)	251-337	Week 37 (Day 253)	223-283
	Week 65 (Day 449)	404-497	Week 65 (Day 449)	419-479
			Week 85 (Day 589)	559-619

4.3 Software

All report outputs will be produced using SAS® version 9.3 or a later version in a secure and validated environment. SF-36 scoring will be calculated by using Quality Metric PRO CoRE Smart Measurement System, PRO CoRE Version 2.1.

4.4 Study Subjects

4.4.1 Disposition of Subjects

The number of patients screened, the number and percentage of patients enrolled, the number and percentage of patients treated and who completed the study, the number and percentage of patients who discontinued from treatment, and the number and percentage patients who withdrew from study, including the main reasons for screen failure and reasons for discontinuation/withdrawal, will be summarized. The percentage of patients enrolled will be calculated based on the number of patients screened. The percentage of patients treated, the percentage of patients who discontinued from treatment, and the percentage of patients who withdrew from study will be calculated based on the number of patients enrolled. The percentage of the reasons for discontinuation from treatment and withdrawal from study will be based on the number of patients who discontinued from treatment and withdrew from study, respectively. A corresponding by-patient listing will also be provided.

4.4.2 Protocol Deviations

Protocol deviations will be identified as major/minor prior to database lock.

Major protocol deviations will be summarized by deviation category. Additionally, protocol deviations related to COVID-19 will also be summarized by deviation category.

4.5 Analysis Sets

The population definitions that will be used in this study are provided below and are very similar to those employed in the NEURO-TTR trial. The number of patients in each analysis population will be summarized by treatment group and overall for all randomized patients.

4.5.1 Screened Patients

Screened patients will be defined as those patients who signed an informed consent form. Screen failures and reason for failure will be summarized.

4.5.2 Randomized Set

The Randomized Set will be defined as those screened patients who received a randomization assignment. Results will be summarized under the treatment to which patients were randomized.

4.5.3 Full Analysis Set (FAS)

The Full Analysis Set will be defined as all randomized patients who received at least 1 injection of ION-682884 or inotersen and who have a Baseline and at least 1 post-Baseline efficacy assessment for mNIS+7 score or Norfolk QOL-DN questionnaire total score. For the NEURO-TTR trial, the FAS included all randomized patients who received at least 1 injection of study drug and who had a Baseline and at least 1 post-Baseline efficacy assessment for the mNIS+7 score or Norfolk QOL-DN questionnaire total score. The FAS will be the primary population for analysis of efficacy and PD outcomes. Results will be summarized under the treatment to which patients were randomized.

It is possible that the Week 66 final analysis FAS might be slightly different from the Week 35 interim analysis FAS.

4.5.4 Per Protocol Set (PPS)

The Per Protocol Set is defined as those patients from the FAS who received at least 80% of prescribed injections of ION-682884 or inotersen and who have no significant protocol deviations that would be expected to affect efficacy assessments. The PPS will be defined separately for Week 35 interim analysis and Week 66 final analysis. The Week 35 interim analysis PPS will use only data up to week 35 while the Week 66 final analysis PPS will use all data up to Week 66.

Summary of reasons for patients excluded from PPS will be provided. Results will be summarized under the treatment to which the patients were randomized.

4.5.5 Safety Set

The Safety Set (SS) will be defined as all patients who are randomized and receive at least 1 dose of ION-682884 or inotersen. For the NEURO-TTR trial, the SS included all randomized patients who received at least 1 injection of study drug. Results will be summarized under the treatment which the patients received.

4.5.6 PK Set

The PK Set will be defined as all patients who are randomized and receive at least 1 dose of ION-682884 or inotersen and have at least 1 evaluable PK sample. Results will be summarized under the treatment which the patients received.

PK Subgroup: patients who will have additional PK samples collected on Days 1, 225 (Week 33) and 449 (Week 65). Results will be summarized under the treatment which the patients received.

4.6 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be descriptively summarized by treatment group for the Randomized Set, FAS, PPS, SS, and PK. Patient's allocation by investigative site will be tabulated by treatment group and overall for the all enrolled patients.

The following summary and listing will be provided:

Patient demographic characteristics and Baseline severity of illness will be summarized by treatment group and overall for the Randomized Set, SS, FAS, PPS, and PK Set. Patient demographic characteristics, including age, age group (<65 years, 65-74 years, >=75 years), sex, race, ethnicity, country of site, TTR genotype category, duration of disease from hATTR-PN diagnosis (months), and duration from onset of hATTR-PN symptoms (months), criteria used to document the diagnosis of TTR cardiomyopathy (FAC), duration of disease from FAC diagnosis (months), and duration from onset of FAC symptoms (months), previous treatment and disease stage will be summarized by treatment group and overall for the SS, FAS, PPS, and PK subgroup. Baseline severity of illness, including the NIS score, mNIS+7, PND score, serum TTR, high-sensitivity Troponin T, mBMI, BMI, weight, height, NYHA, and NT-proBNP, will be summarized by treatment group and overall for the SS, FAS, PPS and PK subgroup. Measures of quality of life and level of functioning, including the baseline Norfolk QOL-DN total score and SF-36, will also be included.

The TTR genotype category will be summarized by V30M vs. Non-V30M. The V30M genotype category includes V30M Mutation ('Yes') and VAL50MET, V50M MUTATION, V50M and P.VAL50MET listed under the "Other" category in CRF.

The hATTR-PN/FAC diagnosis and onset date of hATTR-PN/FAC symptoms only collected year and month information in CRF. To facilitate the calculation of duration, the following imputation rules will be applied:

- If year is missing, no imputation will be performed.
- Day will be imputed as 01.
- If month is missing and the recorded year is before the year in informed consent date, the missing month will be imputed to be December; otherwise, it will be imputed as the month from the informed consent date.

A by-patient listing of demographics will be presented based on the SS. This will include the year of birth, age (in years), sex, race, ethnicity, height (in cm), weight (in kg) and BMI. The body weight will be the measurement obtained at Screening.

4.7 Medical History

Medical history will be coded by Medical Dictionary for Regulatory Activities (MedDRA) dictionary Version 25.0 or later version and will be summarized by system organ class (SOC) and preferred term (PT), by treatment group and overall for the SS. Medical history will also be provided in the data listings.

In addition, the CRF has a page for medical history of interest prompt. All medical history of interest collected in this CRF will be listed.

4.8 Concomitant Medication

Medications will be coded using Anatomical Therapeutic Chemical (ATC) Classification codes by WHODRUG Global B3 Mar2022 or later.

Prior and concomitant medications will be defined using the start and stop dates, and ongoing fields recorded in the Case report form (CRF) relative to the first and last dose dates of randomized study drug. A prior medication is defined as any medication taken up to, but not including the start date of study drug. A concomitant medication is defined as any medication taken whilst study drug is being taken.

Note that if either of the start dates or stop dates of prior/concomitant medication are missing, the worst, i.e. most conservative, case will be considered when slotting medications (i.e., the medications should slot into all possible phases). If a medication is administered pre-treatment or after first dose of study drug and no stop date/time is recorded, then usage will be assumed to be ongoing for the remainder of the data collection periods. If a medication is stopped on treatment or after first dose and no start date/time is recorded, it will be assumed that the medication was ongoing from prior to the start of study drug. If a medication has no start or stop date, it will be assumed that the medication was ongoing from prior to the start of study drug. 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 prior, concomitant medication defined relative to use of study drug are shown schematically in the diagram below.

Scenario	First dose date	Prior Medication	Concomitant
1	x----------x |	Y	N
2	x----------x/*	Y	Y
3	| x-------x/*	N	Y
4	?----------x |	Y	N
5	?----------x/*	Y	Y

Scenario	First dose date		Prior Medication	Concomitant
6	x----------?		Y	Y
7		x----------?/*	N	Y

CM = concomitant medication
x = start/stop date/time
? = missing date/time
*= ongoing

4.9 Treatment Exposure and Compliance

Exposure to study drug will be summarized for the Safety Set by treatment duration (weeks), total volume (mL) and total dose administered. The reason for dose pause will be tabulated. A listing summarizing for each subject the number of dose reductions (frequency of administered dose < protocol defined dose) and missed doses (injection not givens) will be provided. Doses that were not given because the patient discontinued study drug will not be summarized.

Duration of study drug exposure will be derived as the difference between the date of the last dose of study drug and the date of the first dose plus one.

Study drug will be administered as SC injections. The total dose of study drug during the treatment period will be computed for subjects receiving ION-682884 or inotersen by summing as following:

- for ION-682884, the administered dose between the first dose of study drug on Day 1 and the EOT date or date of premature treatment discontinuation;
- for inotersen prior to switch, the administered dose between the first dose of study drug on Day 1 and the last dose date before switch or date of premature treatment discontinuation;
- for inotersen switch to ION-682884, the administered dose between the first dose of ION-682884 and the EOT date or date of premature treatment discontinuation ;
- for NEURO-TTR Inotersen, the administered dose between the first dose of study drug on Day 1 and the EOT date or date of premature treatment discontinuation.

Total dose will be summarized in mg. [redacted]

Treatment duration, Treatment duration category (<6 months, ≥ 6 months to < 12 months, ≥ 12 months), amount of ION-682884 or inotersen received, and reasons for discontinuation of ION-682884 or inotersen will be summarized by treatment group (NEURO-TTR Inotersen, ION-682884, inotersen/ION-682884 prior switch and inotersen/ ION-682884 after switch).

ION-682884 will be administered once every 4 weeks [redacted] as a SC injection. Inotersen will be administered once every week [redacted] as a SC injection.

A descriptive summary of treatment compliance variables will be provided:

- Total dose injected (mg)

- Overall treatment compliance by groups (%):

  [Actual total dose infused (mg) in each treatment group /Expected total dose (mg) to be administered in each treatment group] *100. For patients who discontinued treatment, denominator should be (number of doses expected until discontinuation).

  This compliance will be analyzed by following treatment groups:

  - ION-682884
  - inotersen prior to Week 35
  - inotersen switch to ION-682884
  - NEURO-TTR Inotersen

  The overall actual total volume: sum of actual total volume of treatment by subject.

  The overall expected total volume: sum of expected total volume of treatment by subject.

- Treatment compliance by categories (<80%, 80%-100%, 100%-120%, >120%)

Duration of drug exposure (month) and total amount of ION-682884 administered (mg) will be summarized by baseline platelet count categories $< 125 \times 10^9$/L, ≥ 125 to $< 150 \times 10^9$/L, ≥ 150 to $< 175 \times 10^9$/L, ≥ 175 to $< 200 \times 10^9$/L, and $\geq 200 \times 10^9$/L.

4.10 Efficacy Evaluation

4.10.1 Analysis and Data Conventions

TTR

As part of the primary analysis, TTR levels at both baseline and postdosing will be compared to the levels in the placebo arm of the NEURO-TTR trial. During the NEURO-TTR trial, TTR levels in human serum were measured using a validated commercial pre-albumin assay from Roche, using an immunoturbidometric method. In the ION-682884-CS3 trial, a novel electrochemiluminescence (ECL) assay has been developed and validated to measure TTR levels in human serum. In order to enable valid cross-assay comparison of TTR levels from the two assays, a formula was created as part of cross-validation of the two methods, y=0.0057x^2 + 0.5843x - 0.3819 (data and derivation of the formula are provided in the method validation report TTR-BRV02). Accordingly, the immunoturbidometric serum TTR level data from the placebo arm in the NEURO-TTR trial will be converted using the formula y=0.0057x^2 + 0.5843x - 0.3819 to allow comparison to data generated by the current ECL assay. The converted value of the placebo arm data will then be used in the primary analysis.

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 the 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 peripheral nerve assessment of the lower and upper limbs:
  - Nerve Conduction Tests (∑5 NC), maximum 18.6 points from 5 subcomponents (Fibular CMAP amplitude [PMAK], fibular nerve motor conduction velocity [PMCVK], fibular nerve distal latency [PMLA], tibial nerve distal latency [TMLA], and Sural SNAP amplitude [SSAB]), with a minimum of -3.72 points and a maximum of +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).

Due to the testing algorithm and the MC Core data entry conventions, raw modified + 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 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 Medidata Rave EDC database	None
	If HRDB was not measured in error or missing for other reasons, MC Core entered	Set "-9" to missing

Component	Data entry convention /Comment	Pre-processing step
	a "-9" into the Medidata Rave EDC database	
	Transform normal deviate 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, MC Core entered a "-9" into the Medidata Rave EDC database	Set "-9" to missing
	For all 5 subcomponents (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 anatomical site was assessed, MC Core entered a "0", "1" or "2" into the Medidata Rave EDC database	None
	If an anatomical site was skipped because it was assumed to be < 95%, MC Core left the field blank in the Medidata Rave EDC database (the last assessed more distal anatomical site has a "0" entered)	Set blank field to "0"
	If an anatomical site was not tested in error, MC Core entered a "-9" into the Medidata Rave EDC database	Set "-9" to missing
Heat Pain	If an anatomical site was assessed, MC Core entered a "0", "1" or "2" into the Medidata Rave EDC database	None
	If an anatomical site was skipped because it was assumed to be < 95%, MC Core left the field blank in the Medidata Rave EDC database (the last assessed more distal anatomical site has a "0" entered)	Set blank field to "0"
	If an anatomical site was not tested in error, MC Core entered a "-9" into the Medidata Rave EDC database	Set "-9" to missing

Additionally, for HP and TP, the composite scores are calculated by multiplying the sum of the 10 averaged subcomponent scores (defined below) by 2 since assessments are only be performed on one side of body.

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, as 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 0 (no symptoms) to 4 (symptoms in the feet, legs, hands, and arms). The other Questions, except for Questions 31 and 32, are scaled on a 5-point Likert scale, ranging from 0 ("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 comprises 36 items that yield an 8-subscale profile of functional health and well-being, as well as psychometrically-based physical and mental health measures. From 35 of the 36 items, 8 subscales and 2 summary measures are constructed. The 8 subscales are:

- The Physical functioning (PF)
- Role-Physical (RP)
- Bodily pain (BP)
- General health (GH)
- Vitality (VT)
- Social Functioning (SF)
- Role-Emotional (RE)
- Mental Health (MH)

The 2 summary measures are:

- PCS
- Mental component summary (MCS)

Scoring of the PCS and MCS involves three steps: First, the 8 subscales (normalized scores) are standardized using the means and standard deviations. Second, they are aggregated using weights (factor scores coefficients). Finally, all 8 subscales and aggregate PCS and MCS scores are

standardized using a linear T-transformation to have a mean of 50 and a standard deviation of 10 All norms and scoring algorithms used will be based on the US population norms.

PCS and MCS will be set to missing if the patient is missing any of the eight SF-36 scales.

The scoring of the SF-36 will be conducted using the Quality Metric PRO CoRE Smart Measurement System, PRO CoRE Version 2.1.

NSC

The NSC (version: 04Jan2009) questionnaire consists of one total score and five domains (muscle weakness, sensory (hypo/loss of sensation), sensory (paresthesia, hyper sensation), autonomic (gastrointestinal 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 Appendix 6.2.

10MWT

The 10MWT is used to assess walking speed in meters per second (meter/second) over a short distance. It can be employed to assess functional mobility, gait, and vestibular function. The 10MWT can be done in two different ways: comfortable gait speed, or fast walking speed. A lower score indicates worsening.

The time is measured for the middle 6 m to allow for patient acceleration and deceleration:

- the time is started when any part of the leading foot crosses the plane of the 2-meter mark;
- the time is stopped when any part of the leading foot crosses the plane of the 8-meter mark.

The total time taken to ambulate 6 meters (m) is recorded to the nearest hundredth of a second. 6 m is then divided by the total time (in seconds) taken to ambulate. If a patient requires total assistance or is unable to ambulate at all, a score of 0 m/s should be documented.

R-ODS

The R-ODS is a 24-item patient-reported outcome instrument and linearly weighted scale developed to measure the activity and social participation limitations in patients with Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, and gammopathy-related polyneuropathy. The response to each dimension is scored as: 0=not possible to perform, 1=possible but with some difficulty, 2=possible without any difficulty, and lower score indicates worsening disability. This method enables the use of sum scores by creating interval scales revealing the real difference in ability levels between patients and within patients in time.

If any of 24 items is missing, then the summed score will be set as missing.

COMPASS-31

COMPASS-31 is a 31-item questionnaire that evaluates autonomic function across 6 domains: orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor.

Individual questions within domains inquire about symptom frequency (rarely to almost always), symptom severity (mild to severe), and symptom improvement (gotten much worse to completely gone).

Questions include either “yes” or “present” will be scored as 1, “no” or “not present” scored as 0. All questions regarding the frequency of symptoms will be scored as 0 points for “rarely” or

"never", 1 point for "occasionally" or "sometimes", 2 points for "frequently" or "a lot of the time" and 3 points for "almost always" or "constantly". All questions regarding the severity of symptoms will be scored as 1 point for "mild", 2 points for "moderate", and 3 points for "severe". When assessing the time course of a symptom, will be scored 0 points for responses of representing improvement such as "gotten/getting somewhat better", "gotten/getting much better", "completely gone" and "I have not had any of these symptoms", 1 point for "stayed about the same", 2 points for "gotten/getting somewhat worse" and 3 points for "gotten/getting much worse." The scores for changes in bodily functions depended on the individual question asked. For example, "I get full a lot more quickly now than I used to when eating a meal" will be scored 2 points, "I get full more quickly now than I used to when eating a meal" will be score as 1 point, and "I get full less quickly now than I used to", "I get full a lot less quickly now than I used to" will be scored 0 points, while the answer "I sweat somewhat more than I used to", "I haven't noticed any changes" will be given 0 point, "I sweat much more than I used to" and "I sweat somewhat less than I used to" will be given 1 point and "I sweat much less than I used to" will be scored 2 points. A detailed list of can be found in Table 3 of Appendix 6.3.

Depending on the domain, possible scores in each domain ranged from 6 (vasomotor) to 28 (gastrointestinal). Final score is a sum total of all subscales varying from 0 to 100, with higher scores indicating worsening of autonomic dysfunction.

EQ-5D-5L

EQ-5D-5L is a standardized measure of health status developed by the EuroQoL Group to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-5L consists of the EQ-5D-5L descriptive system and the EQ Visual analog scale (VAS).

The EQ-5D-5L descriptive system comprises five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). The response to each dimension is scored as follows: 1=no problems, 2=slight problems, 3=moderate problems, 4=severe problems, 5=unable. Lower score indicates worsening of QOL.

The EQ VAS is used as a quantitative measure of health outcome as judged by the individual respondent. The EQ VAS records a self-rating of health status on a vertical VAS anchored at 100 (best imaginable health state) at the top and 0 (worst imaginable health state) at the bottom.

If any of five dimensions is missing, then the index value will be set as missing.

PGIC

PGIC is a single-item scale. Patients choose the response that best describes the overall change in their amyloidosis condition since they started taking the study medication. Patients rate their change on a 5-point scale as (1) much better, (2) a little better, (3) no change, (4) a little worse, (5) much worse.

If the scale is missing, then PGIC score will be set as missing.

PGIS

PGIS is a single-item scale. Patients choose the response below that best describe the severity of the amyloidosis condition over the past week on a 5-point scale: (0) none, (1) mild, (2) moderate, (3) severe, or (4) very severe.

If the scale is missing, then PGIS score will be set as missing.

4.10.1.1 Multi-center Study

This study will be conducted at multiple centers worldwide. For analyses that include investigative site, the analysis will use pooled sites. All sites with fewer than two randomized patients per treatment group with non-missing baseline and Week 66 mNIS+7 composite scores will be pooled together within the same country and considered as a single site for analysis. If this results in any site with fewer than two randomized patients per pooled site, the smallest site will be pooled with the next smallest site within the same geographic region (North America, Europe, or South America/Australasia/Asia). If there are no other sites in the region, no further pooling will be conducted.

4.10.1.2 Adjustments for Covariates

The primary efficacy analysis will be adjusted for the following covariates measured at Baseline:

- Disease stage (Stage 1/Stage 2)
- V30M mutation (Yes/No)
- Previous treatment (Yes/No)
- Baseline value of endpoint

4.10.1.3 Handling of Dropouts or Missing Data

Composite score: NIS 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 assessment is not conducted at a visit, then the mNIS+7 and the composite, components and subcomponents will be considered as missing at that visit. In a Mixed Model for Repeated Measures (MMRM), missing data are not explicitly imputed. Instead, all available post-Baseline assessments (within the scheduled visit windows) of the endpoint during the treatment period are utilized and via modelling of the within subject correlation structure, the endpoint treatment differences (which are adjusted to take account of missing data) are derived. In addition, several 'Missing not at random' methods are described in Section 4.10.3.2 and will be used as sensitivity analyses to impute missing visit level data.

Missing data imputation strategies for missing assessment level data

Two independent assessments of the primary efficacy endpoint, mNIS+7, are planned at the baseline visit and the Week 66 visit, and at the early termination visit (for patients that terminate treatment early). A single mNIS+7 assessment is also planned at the Week 35 and Week 85 visit. The mean of the two replicate assessments within visit will be used for analysis of both the baseline and Week 66 visits (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. Note, for NIS, an additional step is needed by summing left side and right side averaged score to obtain average subcomponent scores. These will be referred to as the averaged subcomponent scores.

At baseline and Week 66, 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 will be set to missing. At Week 35, only one assessment is performed; therefore, the single subcomponent will be used as the averaged subcomponent score for that visit. These values will be used in the summary and analysis of averaged subcomponent scores.

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.

The component scores will be computed by summing the averaged subcomponent scores, and the composite scores will be computed by summing the component scores.

Imputation of missing averaged subcomponents

If a patient has completed at least part of the mNIS+7 at a visit, then the following imputation method will be used to impute this missing assessment level data for the purpose 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 and B:

- 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 (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 Randomized Set (across treatment groups). The component score is then calculated.
- Step 3 (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 NEURO-TTR placebo in the Randomized Set at that visit. The component score is then calculated.

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 NEURO-TTR placebo can be derived. In order to apply step 3, the following visits will be used to derive the mean scores in the NEURO-TTR placebo group:

Timing of Visit	Imputation rule
Before Week 35	Randomized Set mean at baseline
Between Week 35 and Week 66	Week 35 NEURO-TTR placebo mean

Note: when imputing missing subcomponents based on NEURO-TTR placebo mean at a specific visit, the NEURO-TTR placebo mean is derived from on-treatment assessments only (i.e., those that were done within 52 days of last dose).

The components of the mNIS+7 are grouped into A and B based on the imputation step used, as follows. A detailed list of components by group can be found in Table 1 and Table 2 in Appendix 6.1:

- Group A: For components with multiple subcomponents, imputation steps 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 Nerve Conduction Test [NCT]) are available and only one is missing at that visit, then step 3 will be applied for 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 NEURO-TTR placebo.
  If, after applying steps 1-3 as appropriate, there are still missing subcomponent scores, the component score will be set to missing.
- Group B: component HRDB has only one subcomponent. Missing data for these averaged subcomponents score will be imputed as follows:
  - For Baseline, the missing averaged subcomponent scores will be set to equal to the mean baseline averaged subcomponent score from the Randomized Set (across treatment groups).
  - For 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 NEURO-TTR placebo in the Randomized Set at that visit. 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 NEURO-TTR placebo group can be derived. In order to derive the mean scores in the NEURO-TTR placebo group, the following visits will be used:

Timing of Visit	Imputation rule
Before Week 35	Randomized Set mean at baseline
Between Week 35 and Week 66	Week 35 NEURO-TTR placebo mean

Composite Score

The composite scores of mNIS+7, modified +7, and NIS will each be calculated by summing the imputed component scores. If any of the component scores after imputation are 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: If any question is missing at baseline, the mean value for this question at baseline from the study population (across all

treatment groups) will be used to impute the missing baseline question value. For post-baseline visits during the treatment period, any missing question values will be imputed using the last observed or imputed question value (including 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

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. The mean of the two replicate assessments within a visit will be used for analysis of both the Baseline and Week 66 visits (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 Baseline and Week 66, in the event that only one NSC assessment has been performed, the single NSC assessment will be used in place of the mean value for that visit for the averaged question score. If both of the NSC assessments are missing, the averaged question score is set to missing. At Week 35, only one assessment is performed, therefore the single NSC assessment 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 the 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% of 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.

Pattern of Missing Data

For mNIS+7 and Norfolk QOL-DN composite scores, the pattern of missing data will be explored. Multiple imputation methods (Section 4.10.3.2) will be used to impute missing data in the sensitivity analyses of the primary efficacy endpoint.

Imputation of Missing/Partial Dates

The imputation of partial or missing dates for adverse events are detailed in Section 4.12.1, and prior/concomitant medications Section 4.8. The hATTR-PN /FAC diagnosis and onset date of hATTR-PN /FAC symptoms only collected year and month information in CRF. To facilitate the calculation of duration, the imputation rules are detailed in Section 4.6.

Replicated Data, Unscheduled Visits, and Early Termination Visits

When change from Baseline is assessed, 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, then the change from baseline will be set to missing.

For patients who withdraw, 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 will be presented 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.

4.10.1.4 Data Summary Plan

The table below details what data will be included in the summary and analysis output by endpoint type, and what output is planned for Week 35 interim analysis, Week 66 final analysis, EOT at Week 85 and what output will be updated for the EOS. Data summarized/analyzed at 35 Week interim, 66 Week final analysis, and EOT will be based on data collected up to the date of the data cut. 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; such exceptions will be noted in this SAP. Note: assessments for mNIS+7, NSC, and ophthalmology done early in the treatment period that are used for baseline cannot also be used as an on-treatment assessment.

Endpoint type	Interim Analysis/ Week 66 Analysis	Provide at EOT (End of Week 85)	Update at EOS	Comment/definition
Efficacy Except for PD (TTR), BMI and mBMI	-Listings -On-treatment summary/analysis tables	-Listings -On-treatment summary/analysis tables -Post-treatment summary tables	-Listings -On-treatment summary/analysis tables -Post-treatment summary tables	-On-treatment: First dose date ≤ Date of assessment ≤ Last dose date + 52 days -Post-treatment: Date of assessment > last dose date + 52 days -Visit defined by analysis visit window -The primary inference for mNIS+7 and Norfolk QOL-DN will be made at EOT, even if data slotted in the on-treatment period has changed by EOS
PD (TTR), BMI and mBMI	-Listings -On-treatment - Summary/analysis tables	-Listings -On-treatment -Summary/analysis tables	-Listings -On-treatment -Summary/analysis tables	-On-treatment: First dose date ≤ Date of assessment ≤ Last dose date + 28 days -Post-treatment: Date of assessment > last dose date + 28 days -Visit defined by analysis visit window
ECG, Lab, vital signs (including body weight),	-Listings - Summary/analysis tables	-Listings -Summary/analysis tables	-Listings -Summary/analysis tables	
AE	-Listings - Summary/analysis tables	-Listings -Summary/analysis tables	-Listings -Summary/analysis tables	-
Concomitant/ Prior medications	-Listings - Summary/analysis tables	-Listings -Summary/analysis tables	-Listings -Summary/analysis tables	

Endpoint type	Interim Analysis/ Week 66 Analysis	Provide at EOT (End of Week 85)	Update at EOS	Comment/definition
IM	-Listings - Summary/analysis tables	-Listings -Summary/analysis tables	-Listings -Summary/analysis tables	
PK	-Listings - Summary/analysis tables	-Listings -Summary/analysis tables	-Listings -Summary/analysis tables	

4.10.1.5 Interim Analysis and Multiplicity

An interim analysis will be performed to assess the efficacy and safety profile of ION-682884 compared to the placebo arm of NEURO-TTR when all patients on ION-682884 complete Week 35 assessments.

For the Week 35 interim analysis, there are two co-primary endpoints:

- Serum TTR percent change from Baseline at Week 35.
- mNIS+7 change from Baseline at Week 35.

The Norfolk total score change from Baseline at Week 35 is a secondary endpoint at the interim analysis. Norfolk will only be tested if both primary endpoints are significant.

Regardless of the interim analysis results, the study will proceed as planned, and the data will be collected at Week 66 and further for all study endpoints.

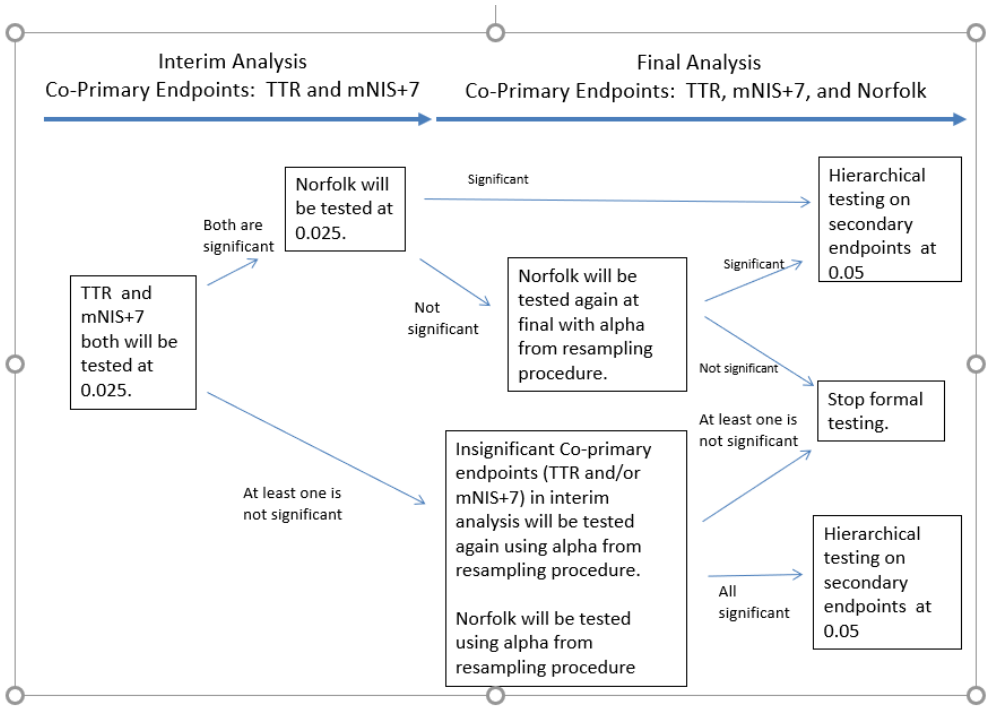
For Week 66 final analysis, there are three co-primary endpoints:

- Serum TTR percent change from Baseline at Week 65
- mNIS+7 change from Baseline at Week 66
- Norfolk total score change from Baseline at Week 66

There are also five secondary endpoints listed as follows in the order of testing sequence,

- NSC change from Baseline at Week 66
- NSC change from Baseline at Week 35
- PCS score of SF-36 change from Baseline at Week 65
- PND change from Baseline at Week 65
- mBMI change from Baseline at Week 65.

The diagram below illustrates the testing procedure for the interim and final analyses.



Week 35 Interim Analysis treatment comparison
Below are the 2 primary treatment comparisons planned in the interim analysis:

- Co-Primary Endpoint: Comparison of percent change from Baseline to Week 35 in the serum TTR between ION-682884 and NEURO-TTR placebo in the FAS
- Co-Primary Endpoint: Comparison of change from Baseline to Week 35 in the mNIS+7 between ION-682884 and NEURO-TTR placebo in the FAS

If both co-primary endpoints of interim analysis (TTR and mNIS+7) are significant at two-sided alpha level of 0.025, then the secondary endpoint (Norfolk) below will be tested at the interim analysis at alpha level of 0.025.

- Secondary Endpoint: Comparison of change from Baseline to Week 35 in the Norfolk total score between ION-682884 and NEURO-TTR placebo in the FAS

Week 66 Final Analysis Treatment Comparison

Week 66 Primary Endpoints Analysis
Below are the 3 primary treatment comparisons planned in the final analysis:

- Co-Primary Endpoint: Comparison of percent change from Baseline to Week 65 in the serum TTR between ION-682884 and NEURO-TTR placebo in the FAS
- Co-Primary Endpoint: Comparison of change from Baseline to Week 66 in the mNIS+7 between ION-682884 and NEURO-TTR placebo in the FAS

- Co-Primary Endpoint: Comparison of change from Baseline to Week 66 in the Norfolk total score between ION-682884 and NEURO-TTR placebo in the FAS

In the Week 66 Final Analysis, for those endpoints that were statistically significant at the Week 35 interim analysis, their corresponding tests at the Week 66 final analysis will not be conducted. The non-significant endpoint(s) (e.g., serum TTR and/or mNIS+7) and the co-primary endpoint Norfolk will be tested at the final analysis. The alpha level of the final analysis for each endpoint will be determined by the resampling procedure (Westfall and Young 1993) as follows.

Let T1 and T2 be the standardized test statistics at the interim and final analyses, respectively. In order to determine the alpha level for the final analysis, the correlation between T1 and T2 is first estimated based on the resampling approach:

- Among the 108 ION-682884 treated patients and 52 NEURO-TTR placebo patients, randomly assign 108 patients to the ION-682884 treated group and 52 patients to NEURO-TTR placebo group.
- Apply the re-randomized treatment assignment to the interim data and obtain the standardized test statistics T1.
- Apply the re-randomized treatment assignment to the final data and obtain the standardized test statistics T2.

Repeat the above procedure N times (N = 10000) and obtain N pairs of test statistics T1 and T2. The correlation between T1 and T2 will then be estimated as the sample correlation of the N pairs.

Let c1 be the cut-off point for the interim 2-sided test corresponding to an alpha of 0.025. Once the estimated correlation ρ is available, the cut-off point c2 for the final analysis is obtained by solving the nonlinear equation $Pr(|T1| \geq c1 \text{ or } |T2| \geq c2) = 0.05$, where (T1, T2) follow a bivariate normal distribution with mean vector (0, 0), standard deviations of 1 and correlation ρ. See Appendix 6.4 for the sample programming code for alpha used in the final analysis.

Week 66 Secondary Endpoint Analysis

If all the co-primary endpoints are significant, the following secondary endpoints, which are not planned to be tested in the interim analysis, will be tested in the final analysis at a 2-sided alpha level of 0.05. The multiplicity will be controlled by using the ranking strategy in the following testing sequence:

- Secondary Endpoint: Comparison of change from Baseline to Week 66 in the NSC between ION-682884 and NEURO-TTR placebo in the FAS
- Secondary Endpoint: Comparison of change from Baseline to Week 35 in the NSC between ION-682884 and NEURO-TTR placebo in the FAS
- Secondary Endpoint: Comparison of change from Baseline in the PCS score of SF-36 at Week 65 between ION-682884 and NEURO-TTR placebo in the FAS
- Secondary Endpoint: Week 66 Final Analysis: Comparison of change from Baseline to Week 65 in the PND between ION-682884 and NEURO-TTR placebo in the FAS
- Secondary Endpoint: Comparison of change from Baseline to Week 65 in mBMI between ION-682884 and NEURO-TTR placebo in the FAS

4.10.2 Primary Efficacy Variable

4.10.2.1 Primary Endpoint Analysis at Interim Analysis

Below are the 2 primary endpoint analyses for interim analysis:

- Comparison of percent change from Baseline to Week 35 in the serum TTR between ION-682884 and NEURO-TTR placebo in the FAS
- Comparison of change from Baseline to Week 35 in the mNIS+7 between ION-682884 and NEURO-TTR placebo in the FAS

The significance level of two-sided 0.025 will be used for both comparisons.

As noted in the Section 4.10.1, the TTR level from the Placebo arm in the NEURO-TTR trial will be converted using the following formula to match data generated by the current assay y=0.0057x^2+0.5843x-0.3819. The converted value will be then used in the primary analysis.

The percent change in serum TTR from Baseline to Week 35 will be analyzed using the MMRM model adjusted by propensity score weights. The MMRM model will also include the effects of treatment (ION-682884 or NEURO-TTR placebo), time (categorical), disease stage (Stage 1/Stage 2), V30M mutation (Yes/No), and previous treatment with Vyndaqel® or Diflunisal (Yes/No), treatment-by-time interaction, baseline value of the endpoint, and the baseline-by-time interaction. The propensity score will be calculated for each NEURO-TTR placebo or ION-682884 patient using a logistic regression model with covariates including disease stage (Stage 1/Stage 2), V30M mutation (Yes/No), and previous treatment with Vyndaqel® or Diflunisal (Yes/No).

Model parameters and treatment effects could be estimated by the following example SAS code:

```
PROC LOGISTIC data=xxx;
CLASS trtp distac pretrtc v30ttrc ;
MODEL trtp (event="ION-682884")=distac pretrtc v30ttrc ;
OUTPUT out=Propensity_Scores pred=pred;
run;

PROC MIXED data=xxx;
CLASS trtp visit usubjid distac pretrtc v30ttrc;
MODEL endpoint=trtp distac pretrtc v30ttrc baseline visit visit*baseline visit*trtp /
DDFM=kr;
REPEATED visit / SUBJECT=usubjid TYPE=un;
LSMEANS visit*trtp / CL DIFF;
Weight wt;
RUN;
```

The ATT (average treatment effect for treated) approach will be used with weight: =1 for subjects in the 682884-CS3 treated group; pred/(1-pred) for subjects in the NEURO-TTR placebo control group

In this model, missing data are not explicitly imputed. Instead, all available post-baseline assessments up to the Week 35 endpoint during the treatment period (which fall in the visit windows) for subjects in the FAS are utilized, and via modelling of the within-subject correlation structure, the endpoint treatment differences (which are adjusted to take account of missing data) are derived. The estimation of treatment differences is based upon the assumption that the missing

data follows a missing at random mechanism (i.e., the missingness of the observations may be dependent on the observed outcomes or covariates, but not on unobserved outcomes).

An unstructured variance-covariance matrix will be used to model the within-patient errors, and the degrees of freedom will be determined using Kenward-Roger method (Kenward, M. G. and Roger, J. H. (1997)). If there are convergence issues with the model, the six methods below will be conducted in the following sequence to solve the convergency issues.

1) SCORING=4 option could be used in the PROC MIXED statement in SAS. This will direct SAS to use the Fisher scoring with the first 4 iterations.
2) TYPE = FA0(t) option will be used where t is the dimension of covariance matrix.

   Sample SAS Code:

```
PROC MIXED data=xxx;
CLASS trtp visit usubjid distac pretrtc v30ttrc;
MODEL endpoint=trtp distac pretrtc v30ttrc baseline visit visit*baseline
visit*trtp / DDFM=kr;
REPEATED visit / SUBJECT=usubjid TYPE= FA0(t); *where t is the dimension
of covariance matrix;
LSMEANS visit*trtp / CL DIFF;
Weight wt;
RUN;
```

3) A heterogeneous compound symmetry covariance structure (TYPE=csh) will be used with robust "sandwich" estimator for the standard errors of the fixed effects parameters.

   Sample SAS Code:

```
PROC MIXED data=xxx empirical;
CLASS trtp visit usubjid distac pretrtc v30ttrc;
MODEL endpoint=trtp distac pretrtc v30ttrc baseline visit visit*baseline
visit*trtp / DDFM=kr;
REPEATED visit / SUBJECT=usubjid TYPE=csh;
LSMEANS visit*trtp / CL DIFF;
Weight wt;
RUN;
```

4) A heterogeneous first-order autoregressive AR(1) structure (TYPE=arh(1)) will be used with robust "sandwich" estimator for the standard errors of the fixed effects parameters.
5) A homogeneous compound symmetry covariance structure (TYPE=cs) will be used with robust "sandwich" estimator for the standard errors of the fixed effects parameters.
6) A homogeneous first-order autoregressive AR(1) structure (TYPE=ar(1)) will be used with robust "sandwich" estimator for the standard errors of the fixed effects parameters.

The treatment contrast for each post-baseline visit up to Week 35 will be estimated by the model, with the Week 35 estimate considered the primary for the interim analysis. The normality assumptions for the MMRM models will be formally tested using a Shapiro-Wilks test at the 0.01 significance level and assessed by inspection of the following plots:

- Histogram of marginal studentized residuals derived from the MMRM model.
- Normal probability plot.

If the Shapiro-Wilks test assessing normality of the MMRM residuals is statistically significant at the 0.01 level, a stratified Wilcoxon rank sum test will be provided and the result will be considered as Primary Analysis for TTR.

The mNIS+7 is scheduled to be assessed at Week 35, Week 66, and Week 85.
Because only 1 post-Baseline assessment (Week 35) is available at Week 35 Interim Analysis, the treatment comparison at Week 35 will be based on the analysis of covariance (ANCOVA) model adjusted by propensity score. The Analysis of covariance (ANCOVA) model will also include the effects of treatment (ION 682884 or NEURO-TTR placebo), disease stage (Stage 1/Stage 2), V30M mutation (Yes/No), and previous treatment with Vyndaqel® or Diflunisal (Yes/No), and the baseline value of the endpoint. Patients with a missing mNIS+7 at Week 35 will have value multiple imputed using an imputation model (Based on MAR assumption) that contains the following variables: disease stage (Stage 1/Stage 2), V30M mutation (Yes/No), previous treatment with Vyndaqel® or Diflunisal (Yes/No), and the Baseline value of the endpoint and the multiple imputation will be stratified by treatment group (Schafer 1997; Schafer 1999). The details are provided in Section 4.10.3.2. Of note, multiple imputation here is treated as primary analysis, which will be based on on-treatment data for Full Analysis Set. In addition, ANCOVA based on observed data (with missing value) will be treated as sensitivity analysis (please see Sensitivity Analysis 8).

Similarly to MMRM above, if the Shapiro-Wilks test assessing normality of the ANCOVA residuals is statistically significant at the 0.01 level, a stratified Wilcoxon rank sum test will be provided.

4.10.2.2 Secondary Endpoint Analysis at Interim Analysis

If both co-primary endpoints of interim analysis (TTR and mNIS+7) are significant at alpha level of two-sided 0.025, then the secondary endpoint (Norfolk) below will be tested at the interim analysis at alpha level of 0.025.

- Secondary Endpoint: Comparison of change from Baseline to Week 35 in the Norfolk total score between ION-682884 and NEURO-TTR placebo in the Full Analysis Set

Similarly to mNIS+7, because only 1 post-Baseline Norfolk assessment (Week 35) is available at Week 35 interim analysis, the same analysis of mNIS+7 will be applied for Norfolk.

4.10.2.3 Primary Analysis at Week 66 Final Analysis

Below are the 3 primary treatment comparisons planned in the Week 66 final analysis:

- Co-Primary Endpoint: Comparison of percent change from Baseline to Week 65 in the serum TTR between ION-682884 and NEURO-TTR placebo in the FAS
- Co-Primary Endpoint: Comparison of change from Baseline to Week 66 in the mNIS+7 between ION-682884 and NEURO-TTR placebo in the FAS
- Co-Primary Endpoint: Comparison of change from Baseline to Week 66 in the Norfolk total score between ION-682884 and NEURO-TTR placebo in the FAS

In the Week 66 Final Analysis, for those statistically significant endpoints at the Week 35 interim analysis, their corresponding tests at the Week 66 final analysis will not be conducted. The non-significant endpoint(s) (serum TTR and/or mNIS+7) and the co-primary endpoint Norfolk will be tested at the final analysis. The alpha level of the final analysis for each endpoint will be determined by the resampling procedure (see Section 4.10.1.5).

For percent change from Baseline of TTR at Week 65, change from Baseline of mNIS+7 at Week 66, and change from Baseline of Norfolk QOL-DN at Week 66, a MMRM model adjusted by propensity score weights will be used. Similar to the interim analysis for TTR, the MMRM model will include the effects of treatment (ION-682884 or NEURO-TTR placebo), time (categorical), disease stage (Stage 1/Stage 2), V30M mutation (Yes/No), and previous treatment with Vyndaqel® or Diflunisal (Yes/No), treatment-by-time interaction, baseline value of the endpoint, and the baseline-by-time interaction. The propensity score will be calculated using the same logistic regression model in the primary analysis (Section 4.10.2.1). In this model, missing data are not explicitly imputed. Instead, all available post-baseline assessments up to the Week 65 (or Week 66) endpoints during the treatment period (which fall in the visit windows) for subjects in the FAS are utilized and via modeling of the within subject correlation structure, the endpoint treatment differences (which are adjusted to take account of missing data) are derived.

4.10.3 Additional Analyses of Primary Endpoints

4.10.3.1 Sensitivity Analyses

In addition to the primary efficacy analysis performed in either interim analysis or final analysis, the following sensitivity analyses will be conducted on the FAS and for each endpoint (TTR, mNIS+7, Norfolk) performed in the Week 35 interim analysis and Week 66 final analyses, except where noted:

- **Sensitivity Analysis 1** (Non-Parametric Analysis). The non-parametric stratified Wilcoxon rank sum test will also be performed for the primary study endpoints adjusted by stratified propensity score weights as the sensitivity analysis. The stratum will consist of 4 quartiles levels of the propensity scores (<=Q1, >Q1 and <= Median, > Median and <=Q3, > Q3). Hodges-Lehmann estimates of the differences between ION-682884 group and NEURO-TTR placebo group based on the Wilcoxon Rank Sum Test will also be provided. The propensity score will be calculated using the same logistic regression model in the primary analysis (Section 4.10.2.1). This sensitivity analysis will be applied for each analysis (TTR, mNIS+7, Norfolk) performed in the Week 35 interim analysis and Week 66 final analyses.

Sensitivity analyses will be performed to investigate the impact of alternative missing data assumptions (Multiple imputation, see Section 4.10.3.2). All assessments that are within the analysis windows are included, even if conducted more than 52 days after last dose. These sensitivity analyses will be applied for serum TTR in the Week 35 interim analysis and serum TTR, mNIS+7, and Norfolk in Week 66 final analyses. These analyses will be done on the Safety Set and will be labeled as:

- **Sensitivity Analysis 2** – Multiple Imputation assuming Missing at Random (MAR)

- **Sensitivity Analysis 3** – Multiple Imputation assuming Copy Increments from Reference (CIR)
- **Sensitivity Analysis 4** – Multiple Imputation assuming Jump to Reference (J2R)

- **Sensitivity Analysis 5** (PPS) – The primary efficacy analysis will be repeated, using the PPS population. This sensitivity analysis will be applied for each analysis (serum TTR, mNIS+7, Norfolk) performed in the Week 35 interim analysis and Week 66 final analyses.
- **Sensitivity Analysis 6** (Responder Analysis) – 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. A responder is defined as a patient whose mNIS +7 score change from baseline to Week 66 is less than or equal to the threshold value. Thresholds that will be tested will include -2, 0, 2, 4, 6, 8, 10 points above the baseline value. For each of these specific response thresholds, the response rates at Week 66 for both the ION-682884 treated group and the NEURO-TTR placebo group will be calculated and plotted against the response threshold. Patients that terminate treatment early irrespective of the reason or that had missing Week 66 data will be considered a non-responder.

  This sensitivity analysis will also be applied for mNIS+7 performed in the Week 35 interim analysis using change from baseline to Week 35.

  Same responder analysis will also be presented for Norfolk for both Week 35 interim analysis and Week 66 final analysis.

- **Sensitivity Analysis 7** (Propensity Analysis using 6 covariates). Additional ANCOVA/MMRM model will also be performed for the primary endpoints adjusted by propensity score weights as the sensitivity analysis. In addition to 3 factors (Disease Stage, V30M, and Previous treatment) used in the logistic model for propensity score in the primary analysis, this sensitivity analysis will include additional 3 covariates (6 covariates total) below:
  - Gender (Male, Female)
  - Modified BMI baseline (continuous value)
  - Region (Europe, North America, South America/Australia/Asia)

- **Sensitivity Analysis 8** (Observed data - ANCOVA) - The same ANCOVA in the primary analysis will be performed based on observed data for mNIS+7 and NORFOLK for Week 35 Interim analysis.

4.10.3.2 Multiple Imputation Methodology

First, a repeated measures Gaussian model will be fitted to the data using a Bayesian approach, with non-informative priors for the mean and variance-covariance matrix to provide a joint posterior for the parameters in this model. The repeated measures Gaussian model will include separate mean profiles for each treatment group and the same covariates as those in the primary MMRM analysis for final analysis and TTR at interim analysis based on on-study data for Safety Set.

For mNIS+7 and NORFOLK at interim analysis, the same ANCOVA model used in the primary analysis will be used in multiple imputation based on on-treatment data for Full Analysis Set.

Independent samples will then be drawn from the posterior distributions for the mean and variance-covariance matrix to provide inputs into an imputation model. For each subject with missing data, these sampled values of the parameters for mean vectors and the variance- covariance matrices specify a joint distribution for their observed and unobserved outcome data.

The post-withdrawal part of each pattern-specific distribution will be modelled using three different approaches discussed below. This imputation model will have the same covariates as those in the primary MMRM analysis.

Based on this imputation model, a single set of data will be sampled for the missing data based on the distribution for the subject's missing data conditional upon their observed data.

The post-withdrawal part of each pattern-specific distribution will be modelled using these three approaches:

1. MAR approach.

The means and variance-covariances following withdrawal are chosen to reflect the subject's own treatment group. This approach should provide similar numerical results to the primary analysis. For Final analysis and TTR at Week 35 interim analysis, all assessments that are within the analysis windows are included in this analysis, even if conducted more than 52 days after last dose (On-Study). For mNIS+7 and NORFOLK at Week 35 interim analysis, only data within 52 days after last dose (On-Treatment) will be included.

2. CIR approach.

The CIR approach is detailed in Carpenter et al. (2013) and addresses a potential pattern of informative missingness where the assumption is that the active Study Drug halts or slow disease progression, and the disease progresses after treatment is discontinued. In CIR, missing data in the NEURO-TTR placebo group will be imputed under a within-treatment arm MAR assumption. For patients in the 682884-CS3 treatment group (ION-682884), their mean profile (i.e., mean increments) will track that of the NEURO-TTR placebo group, but starting from the benefit obtained from the previous visit. All assessments that are within the analysis windows are included in this analysis, even if conducted more than 52 days after last dose.

3. J2R approach.

The J2R approach is detailed in Carpenter et al. (2013) and is an extremely conservative imputation approach that assumes that a patient receiving active Study Drug does not sustain benefit after discontinuation of study drug. In J2R, missing data in the NEURO-TTR placebo group will be imputed under a within-treatment arm MAR assumption. For patients with missing data in the ION-682884 treatment group, their mean response distribution is set to equal that of the NEURO-TTR placebo group. All assessments that are within the analysis windows are included in this analysis, even if conducted more than 52 days after last dose.

For each imputation method used, at least 500 imputed datasets will be generated. The imputed observations in each dataset will be checked to ensure they are within the possible change from baseline range for the particular subject they belong to. If a dataset contains out-of-range values, it

will be discarded and a new dataset will be generated until there are 500 datasets which contain no out-of-range values. Each of 500 imputed data sets will then be analyzed using a simple ANCOVA model at Week 35 and Week 66, and the resulting treatment differences and their standard errors will be combined using Rubin's rules. The ANCOVA model adjusted by propensity score will include the effects of treatment (ION 682884 or NEURO-TTR placebo), disease stage (Stage 1/Stage 2), V30M mutation (Yes/No), and previous treatment with Vyndaqel® or Diflunisal (Yes/No), and the baseline value of the endpoint. Note that in these analyses, efficacy assessments that are within the analysis window but more than 52 days after last dose will be included. This is different from the primary analysis, where data after 52 days from last dose is excluded. The number of imputed datasets may be increased after review of results if the simulation error is considered large.

A random seed to be used by a random number generator with value of 2855 will be used to initiate data imputation for all three methods.

4.10.4 Subgroup Analyses of Primary Endpoints

Subgroup analyses will be conducted for each of the two primary efficacy endpoints in the FAS.

Subgroups defined by the following variables will be evaluated:

- V30M mutation (Yes, No)
- Age (< 65 years, 65-74 years, ≥ 75 years old)
- Race (White, non-White)
- Sex (Male, Female)
- Region (North America, Europe, South America/Australia/Asia)
- Previous treatment with Vyndaqel® or Diflunisal (Yes, No)
- Disease stage (Stage 1, Stage 2)
- FAC Clinical Diagnosis from CRF (Yes, No)
- CM subgroup (Yes, No): CM subgroup (Yes) includes patients with 1) a diagnosis of TTR cardiomyopathy at study entry or 2) baseline interventricular septum thickness >= 13 mm on echocardiogram AND no hypertension or ventricular hypertrophy in past medical history or diagnosed on study AND no two consecutive systolic blood pressure readings of >=150 mmHg at any time during the study (including screening and baseline visits).

For TTR (at Week 35 and Week 65), mNIS+7 (at Week 66) and Norfolk (at Week 66), the MMRM adjusted by propensity score for the change from baseline with include fixed categorical effects for treatment, time, disease stage, V30M mutation, and previous treatment, treatment-by-time interaction, treatment-by-subgroup interaction, and treatment-by-time-by-subgroup interaction. The baseline value of the endpoint and the baseline-by-time interaction will be included as covariates in the model. The treatment-by-subgroup interaction at each timepoint will be tested at the significance level of 0.10. Treatment group differences will be evaluated within each category of the subgroup, regardless of whether the interaction is statistically significant. The propensity

score will be calculated using the same logistic regression model in the primary analysis (Section 4.10.2.1).

For mNIS+7 and Norfolk at Week 35, the ANCOVA adjusted by propensity score for the change from baseline with include fixed categorical effects for treatment, disease stage, V30M mutation, and previous treatment with Vyndaqel® or Diflunisal. The baseline value of the endpoint will be included as covariates in the model. The treatment-by-subgroup interaction will be tested at the significance level of 0.10. Treatment group differences will be evaluated within each category of the subgroup, regardless of whether the interaction is statistically significant. The propensity score will be calculated using the same logistic regression model in the primary analysis (Section 4.10.2.1).

4.10.5 Secondary Efficacy Variables for Week 66 Final Analysis

The secondary endpoints at Week 66 Final Analysis include the following analyses:

- Comparison of change from Baseline to Week 66 in the NSC between ION-682884 and NEURO-TTR placebo in the FAS
- Comparison of change from Baseline to Week 35 in the NSC between ION-682884 and NEURO-TTR placebo in the FAS
- Comparison of change from Baseline in the PCS score of SF-36 at Week 65 between ION-682884 or NEURO-TTR placebo in the FAS
- Comparison of change from Baseline to Week 65 in the PND between ION-682884 and NEURO-TTR placebo in the FAS
- Comparison of change from Baseline to Week 65 in mBMI between ION-682884 and NEURO-TTR placebo in the FAS

Treatment group differences will be evaluated using the same method as the primary efficacy analysis (MMRM described in Section 4.10.2). These analyses will be conducted on both the FAS and the PPS populations. No sensitivity analyses will be conducted.

The normality assumptions for the MMRM will be assessed for each of the secondary endpoints by inspecting the following plots:

- Histogram of marginal studentized residuals derived from the MMRM model.
- Normal probability plot.

The non-parametric stratified Wilcoxon rank sum test may be performed as a sensitivity analysis, if deemed necessary. Hodges-Lehmann estimates of the differences between ION-682884 and NEURO-TTR placebo as well as distribution-free confidence intervals based on the Wilcoxon Rank Sum Test will also be provided.

4.10.6 Pharmacodynamic Analysis

Analyses of PD endpoints will be evaluated using the same method as the primary efficacy analysis (MMRM described in Section 4.10.2). No sensitivity analyses will be conducted except for TTR. All PD analyses will be conducted on both the FAS and the PPS.

Additionally, the proportion of subjects with percentage decrease from baseline in serum TTR <50%, ≥50%, ≥60%, ≥70%, ≥80%, and ≥90% will be summarized by treatment group at each visit.

4.10.7 Exploratory Analyses

Exploratory analyses include the comparisons of change from Baseline in the following parameters:

- mNIS+7
- Norfolk QOL-DN
- 10MWT
- R-ODS
- COMPASS-31
- EQ-5D-5L

For mNIS+7 and Norfolk QOL-DN, descriptive statistics will be provided for absolute values and change from baseline at Week 85.

For 10MWT, R-ODS, COMPASS-31 and EQ-5D-5L, descriptive statistics will be provided for absolute values and change from baseline at Week 37 and Week 81.

For PGIC and PGIS, descriptive statistics will be provided for absolute values and change from baseline at Week 37 and Week 81.

Exploratory analyses to evaluate the efficacy of ION-682884 as compared to NEURO-TTR placebo are listed below:

- SF-36 components
- All cause hospitalizations
- Transthoracic ECHO parameters of interest
- NT-proBNP

For SF-36, descriptive statistics will be provided for absolute values and change from baseline at Week 35 for each component.

For NT-proBNP and High-Sensitivity Troponin T, descriptive statistics for original scale and log-transformed will be provided for absolute values and change from baseline at Week 35 and 65.

The change from baseline will be analyzed using an ANCOVA model with fixed effects of treatment, disease stage (Stage 1/Stage 2), V30M mutation (Yes/No), and previous treatment with Vyndaqel® or Diflunisal (Yes/No), and baseline value as covariate based on FAS adjusted by propensity score. The propensity score will be calculated using the same logistic regression model in the primary analysis (See Section 4.10.2.1).

For all cause hospitalizations and all cause hospitalizations in patients with cardiac involvement, summary tables will be provided and Chi-square test will be used for analysis.

Protocol-specified ECHO parameters will be analyzed for patients with baseline wall thickness >15mm using an MMRM model with fixed effects of treatment, disease stage (Stage 1/Stage 2), V30M mutation (Yes/No), and previous treatment with Vyndaqel® or Diflunisal (Yes/No), and baseline value as covariate.

In addition, TTR will be summarized for Inotersen reference arm in 682884-CS3.

4.11 PK and IM Analysis

4.11.1 PK Analysis

4.11.1.1 Plasma Concentration Data

Plasma concentrations of ION-682884 (as total full-length oligonucleotides, including fully, partially, and un-conjugated ION-682884) or inotersen, along with the scheduled (nominal) and actual sampling times (i.e., time from SC dosing) will be listed for each evaluable patient by treatment, actual dose, gender, subject 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.

For all patients who receive ION-682884 and/or inotersen treatment, ION-682884 or inotersen plasma trough and post-treatment concentrations will be summarized using descriptive statistics by treatment, dose, study day, and scheduled time point, without and with stratification by subject IM status (see Section 4.11.3). ION-682884 or inotersen plasma concentrations from the PK subgroup will also be similarly summarized. For the purpose of calculating typical summary descriptive statistics (n, mean, SD, SE, %CV, geometric mean, geometric %CV, median, minimum, and maximum) for plasma concentrations, all BLQ values will be set to zero. Mean plasma concentrations that are below the LLOQ will be presented as BLQ, and the SD, SE, %CV, and geometric %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, ION-682884 or inotersen plasma trough (pre-dose) and post-treatment concentrations versus time (actual) profiles from Study Day 1 up to 729 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 subject immunogenicity status (see Section 4.11.3). For the PK subgroup only, ION-682884 or inotersen plasma concentration versus time (actual) profiles from Study Day 1, from Study Day 225, and from Study Day 449, for each patient, as well as corresponding mean (+SD) plasma concentration versus time (scheduled) profiles (by treatment), will be presented graphically on linear and semilogarithmic scales, without and with stratification by subject immunogenicity status (see Section 4.11.3). 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.

4.11.2 Plasma PK Parameters

Non-compartmental PK analysis of ION-682884 or inotersen will be carried out on each evaluable individual patient data for the PK subgroup following ION-682884 or inotersen treatment, respectively, using Phoenix WinNonlin version 8.3 or higher (Pharsight Corporation, Mountain

View, CA) to determine plasma PK parameters. For calculation of PK parameters, all BLQ values will be set to zero.

For the PK subgroup only, the following plasma PK parameters will be calculated (when applicable and possible) based on actual sampling times:

- Cmax (µg/mL): the maximum observed drug concentration in plasma. Calculated for dosing on Study Days 1, 225, and 449.
- tmax (h): the time at which Cmax occurs. Calculated for dosing on Study Days 1, 225, and 449.
- AUC0-6h (µg•hr/mL): areas under the plasma concentration-time curve from zero time (pre-dose) to 6 hours after the SC administration will be calculated using the linear-up log-down trapezoidal rule following dosing on Study Days 1, 225, and 449.

For all evaluable patients (including subjects participating in the PK subgroup) who have sufficient post-treatment samples collected, the apparent plasma terminal elimination half-life will be calculated as described below:

- $t_{½\lambda z}$ (day): the plasma disposition half-life associated with the apparent terminal elimination phase may be calculated from the equation, $t_{1/2\lambda z} = 0.693/\lambda_z$, based on any evaluable post-treatment data with scheduled collections between Days 589 and 729. A minimum of three data points in the elimination phase will be used to define λ_z, and the correlation of determination values (r^2_adjusted) have to be at or greater than 0.8 and a span of at least 1.5 for the estimate to be accepted. Note: if quantifiable data is only available from just 2 time points, span< 1.5, or r^2_adjusted < 0.8, this parameter may still be determined at the discretion of the pharmacokineticist and will be flagged as such. Note: calculation of this parameter may not be possible in patients rolling into an open-label extension study.

Plasma PK parameters will be listed by treatment, dose, subject ID, subject IM status, and study day; and appropriately summarized (overall and separately for the PK subgroup) using descriptive statistics (n, mean, SD, SE, %CV, geometric mean, geometric %CV, median, minimum, and maximum) by treatment and study day. Additionally, subject IM status stratified (see Section 4.11.3) plasma PK parameters will be similarly summarized). Other stratifications may also be performed if deemed warranted at the discretion of the pharmacokineticist and/or biostatistician.

Exposure-response relationships between selected pharmacodynamic (including but not limited to TTR level, mNIS+7 and Norfolk QOL-DN score) and/or safety measures ((including but not limited to ALT) and PK measures (including but not limited to plasma trough concentrations) at selected time points (e.g., Day 29, Day 85, Day 225, etc.) may also be explored (may include with and without stratification by IM status), where appropriate.

4.11.3 IM Analysis

Samples collected at pre-dose on Study Days 1 (baseline), 29, 85, 225, 337, 449, 589 and 729, including early termination samples for IM assessment will be analyzed for anti-ION-682884 antibodies or anti-inotersen antibodies (ADA) for patients receiving ION-682884 or inotersen,

respectively. After the patients switch to ION-682884 treatment, their samples will be analyzed for both anti-ION-682884 and anti-inotersen antibodies.

4.11.3.1 Sample Level ADA Data

An evaluable sample will be designated 'IM positive' based on both positive screening and confirmation assay results (i.e., confirmed positive result), and otherwise will be deemed 'IM negative'. An unevaluable sample, for example, a sample not being stored properly, or insufficient volume for analysis, will be reported as "unknown". Sample IM results (screen positive/negative, confirmed positive/negative or unknown, and when applicable, titer of anti-ION-682884 or anti-inotersen antibodies) before, during, and after treatment with study drug (sample IM status) will be listed by treatment, dose, and day of collection.

The sample ADA incidence (number) and incidence rate (percent) at each evaluated study time point will be determined and appropriately summarized by treatment and dose as the total number of and percentage of evaluated subjects with sample ADA negative, positive, and unknown status. Furthermore, titer over time will be also appropriately summarized (using descriptive statistics) as median, quartiles (25% and 75%), and range by treatment and dose.

4.11.3.2 Subject Level ADA Data

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

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

- Treatment-Emergent ADA: sum of treatment-induced ADA and treatment-boosted ADA as described below:
    - Treatment-Induced ADA: ADA developed de novo (seroconversion) following biologic drug administration (i.e., formation of ADA any time after the initial drug administration in a subject without pre-existing ADA, i.e., baseline negative ADA)
    - Treatment-Boosted ADA: pre-existing ADA that were boosted to a higher level following biologic drug administration (i.e., any time after the initial drug administration the ADA titer is greater than the baseline titer by a factor of 8-fold or more
- Treatment-Unaffected ADA: pre-existing ADA that were not affected (boosted) following biologic drug administration (i.e., any time after the initial drug administration the ADA titer is 4-fold or less)

- ADATYPE would be not applicable (NA) if the subject overall ADA status is negative.

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

- Subject ADA Status at Baseline (ADASTATB): "Positive" if the subject has Week 1 Day 1 pre-dose sample (baseline) tested as confirmed positive; "Negative" if the subject has Week 1 Day 1 pre-dose sample (baseline) tested as confirmed negative; "Unknown" if the subject has Week 1 Day 1 pre-dose sample (baseline) unevaluable.
- Onset of ADA (TFSTADA): i.e., the first day ADA positive sample observed, will be calculated by: the date of first sample has “positive” sample IM status - first dose date +1. This parameter will be calculated for subjects with positive ADA status overall and subjects with treatment-induced ADA, respectively.
- Last Positive ADA Study Day (TLSTADA): defined as the last positive ADA sample observed from the start of study drug treatment and will be calculated by: the date of last sample has “positive” sample IM status - first dose date +1
- Last IM Sampling Study Day (TLSTSAMP): defined as the last ADA sample collected from the start of study drug treatment and will be calculated by: the date of last sample collected - first dose date +1
- Peak titer (PEAKTIT): the highest titer observed for the subject
- Time to peak titer (TPEAKTIT): the time to reach peak titer will be calculated by: the date of first peak titer observed- first dose date +1
- Total number of ADA Positive Samples (NOPOSAMP): the total number of ADA samples being confirmed positive for the subject
- Total number of ADA Samples evaluated (NOADASAMT): the total number of ADA samples being collected and analyzed successfully with reportable results for the subject

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

Transient ADA response:

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

Persistent ADA response:

- Treatment-induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period of 16 weeks or longer or
- Treatment-induced ADA detected only at the last sampling time point of the study treatment period or at a sampling time point with less than 16 weeks before an ADA-negative last sample.

The subject level ADA prevalence, incidence, and positive ADA response being transient or persistent (if applicable) will be calculated as the number and the proportion (percent) of the study population during the study period by treatment and dose. Subject level IM parameters (as described above) will be listed by treatment and dose for all evaluable subjects, and also appropriately summarized (using descriptive statistics) as median, quartiles (25% and 75%) and range, by treatment and dose. Additionally, Subject level IM parameters will be also summarized for subjects with Treatment-Induced ADA only (i.e., excluding subjects with pre-existing ADA).

4.11.3.3 Evaluation of IM Impact on PK, PD, Efficacy and Safety

The impact of IM on PK, PD, and safety will be evaluated by stratifying plasma PK parameters, plasma trough and post-treatment ION-682884 and inotersen concentrations, PD biomarker levels, selected clinical efficacy endpoints and safety measures by subject ADA status and titer quartiles, summarized using typical descriptive statistics, and presented graphically and/or in tables. Efficacy measures to be stratified by subject ADA status will include but may not be limited to TTR level, mNIS+7 and Norfolk QOL-DN scores. Safety measures to be stratified by subject ADA status will include but may not be limited to AEs, and lab tests for hematology, liver and kidney functions.

Additionally, within subject comparisons on plasma C_{max} and AUC may be conducted in patients from the PK subgroup and presented graphically by subject ADA status and treatment if deemed appropriate (Wang YM, et al, 2016).

Lastly, other stratifications (e.g., based on antibody titer, onset of ADA, subjects with treatment-emergent ADA vs. treatment-unaffected 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.

4.12 Safety Evaluation

All safety summaries will be based upon the SS per the treatment group below:

- NEURO-TTR Placebo
- NEURO-TTR Inotersen
- ION-682884

- Inotersen/ION-682884 prior to switch to ION-682884
- Inotersen/ION-682884 after switch to ION-682884

Additional treatment group (e.g., Inotersen/ION-682884 Total) will be included if applicable. 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.

4.12.1 Adverse Events

Adverse events will be coded using the MedDRA Version 25.0 or later version.

Treatment emergent adverse events (TEAE) are defined as adverse events that occurred or worsened after the first dose. An AE with a completely missing start date will be assumed to be treatment emergent. Note, Scenario 1 below indicates the 'worsened' case.

In addition, if severity of an AE changes during the study, a separate AE will be recorded for each severity on the AE CRF with link. The "first" and "second" AE will be identified based on the AE start date and AE end date. The AE start date of the second record is the AE end date of the first record. These linked events should be compared pairwise based on severity (mild/moderate/severe). Consider three scenarios:

- Scenario 1: The first AE record occurs prior to the first dose, the second AE record occurs on or after the first dose, and the severity increases: Only the second record will be counted as treatment-emergent.
- Scenario 2: The first AE record occurs prior to the first dose, the second AE record occurs on or after the first dose, and the severity decreases: Neither record will be counted as treatment-emergent.
- Scenario 3: Both records occur on or after the first dose: only the most severe AE will be counted as TEAE.

For 682884-CS3 Inotersen/ION-682884 group, TEAEs which first occurred or worsened on or after first dosing date of ION-682884 will be defined as the TEAEs after switch to ION-682884; otherwise, they will be defined as TEAEs before switch to ION-682884.

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. If imputed start date is later than end date (not missing or partial missing), start date will be imputed using end date.

The following summaries will be provided for TEAEs by treatment group:

- An overview of all TEAEs
- A summary table of TEAEs by SOC and PT
- A summary table of TEAEs reported in ≥ 2% of patients (after rounding) in ION-682884 or Inotersen treated group (and greater than placebo group) by SOC and PT
- A summary table of drug-related TEAEs by SOC and PT
- A summary table of drug-related serious TEAEs by SOC and PT
- A summary table of TEAEs by maximum severity, SOC and PT
- A summary table of TEAEs leading to discontinuation of study drug by SOC and PT
- A summary table of SAEs leading to discontinuation of study drug by SOC and PT
- A summary table of TEAEs by time from first dose to event onset (< 6 months, ⩾ 6 months to < 12 months, ⩾ 12 months), SOC and PT
- A summary of death, by SOC and PT

TEAEs will be summarized by subgroups below:

- Age at CS3 screening (<65 years, 65-74 years, >=75),
- Sex (Female and Male),
- Race (White, non-White),
- Region (North America, Europe, and South America/Australasia/Asia),
- V30M TTR mutation (Yes, No),
- Previous treatment with Vyndaqel® or Diflunisal (Yes, No),
- Disease stage (Stage 1 and Stage 2),
- FAC Clinical Diagnosis from CRF (Yes, No),
- CM subgroup (Yes, No) as defined in Section 4.10.4

Results will not be provided for a variable if the overwhelming majority of patients are within one level of the subgroup.

Adverse events in the following categories will be summarized separately:

- Adverse events of special interest
- Other adverse events of interest
- Injection site reaction (ISR) and Local cutaneous reactions at injection site (LCRIS)
- Flu-like reactions

Incidence rate and event rate per 100 patient years of exposure will be presented by PT and SOC for the following events:

- All TEAEs
- Serious TEAE
- TEAE with Severity of Severe
- TEAEs leading to discontinuation of study drug
- Injection site reaction (ISR) and Local cutaneous reactions at injection site (LCRIS)

Incidence rate and event rate per 100 patient years of exposure will be presented by category and preferred term for the following events as well:

- Adverse events of special interest
- Other adverse events of interest
- Flu-like reactions

The formula for Incidence/event rate per 100 patient years of exposure is as below:

- Total exposure for each patient = [complete/discontinuation date or data cutoff date) - the first dose of study drug +1] / 365.25
- Total exposure across all subjects will be the summation of total exposure for each patient.
- Incidence rate per 100 patient years of exposure = (number of subjects with TEAEs /total exposure across all subjects) *100.
- Event rate per 100 patient years of exposure = (number of TEAEs /total exposure across all subjects) *100.

4.12.1.1 Adverse Events of Special Interest (AESI)

AESI, including both serious or non-serious events, is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor could be appropriate. AESI, if defined in the study protocol, are required to be reported by the Investigator to the Sponsor immediately, no more than 24 hours of the Investigator's first knowledge of the event. They are not necessarily those expected to be related to study drug or those most frequently occurring.

AESI defined in this SAP are shown in the table below. Additionally, thrombocytopenia AESI of platelet count < 50 x 10^9/L accompanied by a clinically relevant, bleeding events (MB) or clinically relevant, non-major bleeding events (CRNMB), or platelet count of < 25 x 10^9/L independent of a MB or CRNMB event was defined in the protocol as reportable AESI and should be subject to 15-day expedited reporting by the Sponsor to the regulatory agencies.

AESI	Definition
Thrombocytopenia	• AE with HLT: Thrombocytopenia; or • AE with HLT: platelet analyses
Glomerulonephritis	• AE with PT: Nephritis; or • AE with PT: Glomerulonephritis proliferative; or • AE with PT: Glomerulonephritis acute; or • AE with PT: Glomerulonephritis rapidly progressive; or • AE with PT: C3 Glomerulonephritis; or • AE with PT: Chronic autoimmune glomerulonephritis; or • AE with PT: Glomerulonephritis chronic; or • AE with PT: Fibrillary glomerulonephritis; or • AE with PT: Glomerulonephritis membranoproliferative; or • AE with PT: Glomerulonephritis membranous; or • AE with PT: Glomerulonephritis minimal lesion; or • AE with PT: Henoch-Schonlein purpura nephritis; or • AE with PT: Immune mediated nephritis; or • AE with PT: Immunotactoid glomerulonephritis; or • AE with PT: Lupus nephritis; or • AE with PT: Nephritis allergic; or • AE with PT: Nephrotic syndrome
Ocular adverse events related to vitamin A deficiency	• AE with 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 SMQ: Optic nerve disorders; or • AE within the SMQ: Corneal disorders; or • AE within the SMQ: Retinal disorders.

AE = adverse event; HLT = High Level Term; SMQ = Standardized MedDRA Query; PT = Preferred Term.

4.12.1.2 Other Adverse Events of Interest (OAEI)

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
Renal impairment	AE within the SMQ: Acute renal failure
Abnormal liver function	AE within the SMQ: Drug related hepatic disorders-comprehensive search

Other AEs of interest	Definition
Adverse events at the injection site	AE with HLT: Injection site reaction; or AE with HLT: Administration site reaction NEC
Flu-like symptoms	• AE with PT Influenza like illness; or • AE with PT Pyrexia (or Feeling hot or Body temperature increased) plus at least one of the following symptoms: 1. Chills 2. Myalgia 3. Arthralgia 4. Malaise 5. Fatigue 6. Headache 7. Nausea Note that only events that start on the day of the injection or the day after injection will be included.
Central Nervous System (CNS) disorders	AE with SOC: Nervous system disorders
Haemorrhages	AE within the SMQ: Haemorrhages
Cardiac disorders	SOC with Cardiac Disorders, or AE with PTs below under "Investigations" SOC • Investigations 10007612 Cardiac troponin I increased • Investigations 10007613 Cardiac troponin T increased • Investigations 10050528 Ejection fraction decreased • Investigations 10014383 Electrocardiogram QT corrected interval prolonged
Reduced thryroxine	AE within SMQ: Hypothyroidism

Haemorrhages results will be further classified by type of event, using the following categories: actual bleeds, hematomas/subdermal bleeds, investigations SOC (test result), and conditions associated with acquired alterations in hemostasis. Events classified as actual bleeds or hematomas/subdermal bleeds will be further categorized by whether the event occurred at injection site or not at injection site.

4.12.1.3 Injection Site Reaction (ISR) and Local Cutaneous Reactions at Injection Site (LCRIS)

Injection Site Reaction (ISR) defined as TEAEs with MedDRA preferred terms contains text "Injection site". ISR will be summarized by SOC and PT. In addition, ISR will be summarized by SOC, PT and injection location which is the location of the last injection prior to AE onset.

The following MedDRA preferred terms are determined by the Sponsor's Pharmacovigilance personnel to represent the Local Cutaneous Reactions at Injection Site (LCRIS):

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

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.

LCRIS will be summarized by SOC and PT.

Percentage of injections leading to LCRIS will also be summarized. Percentage of injections leading LCRIS 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.

4.12.1.4 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:
    1. Chills
    2. Myalgia
    3. Arthralgia

Only events that start on the day of injection or the day after injection will be included.

The number and percentage of patients overall and by 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.

4.12.1.5 Renal Safety

TEAEs in the MedDRA Acute renal failure SMQ (broad version), Nephropathies High Level Group Term (HLGT), Renal disorders NEC High Level Term (HLT), and Renal failure and impairment HLT, and any of following PTs are related to renal safety.

- Nephritis
- Glomerulonephritis proliferative
- Glomerulonephritis acute
- Glomerulonephritis rapidly progressive
- C3 Glomerulonephritis
- Chronic autoimmune glomerulonephritis
- Glomerulonephritis chronic
- Fibrillary glomerulonephritis
- Glomerulonephritis membranoproliferative
- Glomerulonephritis membranous
- Glomerulonephritis minimal lesion
- Henoch-Schonlein purpura nephritis
- Immune mediated nephritis
- Immunotactoid glomerulonephritis
- Lupus nephritis
- Nephritis allergic
- Nephrotic syndrome

A by-subject listing will be presented for those events.

Number and percentage of subjects with events above will be provided.

Kaplan-Meier plots for time from Day 1 of ION-682884 to first events above will be presented if there are sufficient number of events to make this feasible.

4.12.2 Clinical Laboratory Evaluation

Laboratory tests to ensure patient safety include chemistry panel, complete blood count with differential, thyroid panel, coagulation panel, immunogenicity, inflammatory panel, and urinalysis. For continuous laboratory tests, absolute values, change and percent change from Baseline will be summarized by visit and treatment group. No statistical comparisons between treatments will be conducted for these summaries. Except for platelet counts, only central lab data will be summarized in tables and figures. For platelet count, results from central and local laboratories will be included.

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 Analysis Data Model (ADaM) dataset and will include all central lab records. The local lab listing will be based on the Study Data Tabulation Model (SDTM) dataset. A separate listing for platelets that includes assessment from both the local and central labs will be provided. A separate listing will contain only values outside of normal ranges.

Unless otherwise specified, if the lab value with symbols (e.g., <, >, >=, <=, and ?), the symbol will be removed and the numerical value will be used for tables and figures. The original values with symbol will be used in the listings.

Except for ALT, AST, ALP, Bilirubin, Platelet and eGFR (see Section 4.12.2.1- 4.12.2.3), Selected laboratory parameters were classified by Common Terminology Criteria for Adverse Events (CTCAE v5.0) grade (Appendix 6.5). Shift tables from ION-682884 Baseline to worst post-treatment value will be provided. In addition, shift table for confirmed nadir hemoglobin will be presented.

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 laboratory value is based on consecutive lab values within 7 days. If that value is in the same or worse category the initial value is confirmed. If the consecutive value is in a better category then the initial value is confirmed in the better 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.

Selected central laboratory test results will be graphed by value (include scheduled and unscheduled visit) for individual patients (spaghetti plots over time). Results from both central and local laboratory for platelets will be included in the spaghetti plot. In addition, mean (±SE) by visit plot will be presented.

4.12.2.1 Hepatobiliary Laboratory abnormalities

The number and percentage of patients falling in each of the following categories based on post-baseline assessments will be provided:

- Alanine aminotransferase (ALT) ≥ 3 x Upper limit of normal (ULN)
- ALT ≥ 5 x ULN
- ALT ≥ 8 x ULN
- ALT ≥ 10 x ULN
- ALT ≥ 20 x ULN
- Aspartate aminotransferase (AST) ≥ 3 x Upper limit of normal (ULN)
- AST ≥ 5 x ULN
- AST ≥ 8 x ULN

- AST ≥ 10 x ULN
- AST ≥ 20 x ULN
- Confirmed ALT ≥ 3 x ULN
- Confirmed ALT ≥ 5 x ULN
- Confirmed ALT ≥ 8 x ULN
- Confirmed ALT ≥ 10 x ULN
- Confirmed ALT ≥ 20 x ULN
- Confirmed AST ≥ 3 x ULN
- Confirmed AST ≥ 5 x ULN
- Confirmed AST ≥ 8 x ULN
- Confirmed AST ≥ 10 x ULN
- Confirmed AST ≥ 20 x ULN
- ALT ≥ 3 x ULN - < 5 x ULN
- ALT ≥ 5 x ULN - < 10 x ULN
- ALT ≥ 10 x ULN - < 20 x ULN
- AST ≥ 3 x ULN - < 5 x ULN
- AST ≥ 5 x ULN - < 10 x ULN
- AST ≥ 10 x ULN - < 20 x ULN
- Confirmed ALT ≥ 3 x ULN - < 5 x ULN
- Confirmed ALT ≥ 5 x ULN - < 10 x ULN
- Confirmed ALT ≥ 10 x ULN - < 20 x ULN
- Confirmed AST ≥ 3 x ULN - < 5 x ULN
- Confirmed AST ≥ 5 x ULN - < 10 x ULN
- Confirmed AST ≥ 10 x ULN - < 20 x ULN
- ALT ≥ 3 x ULN or ≥2 x ALT Baseline if ALT Baseline > ULN
- AST ≥ 3 x ULN or ≥2 x AST Baseline if AST Baseline > ULN
- Confirmed ALT ≥ 3x ULN or confirmed ALT ≥ 2 x ALT Baseline if ALT Baseline > ULN
- Confirmed AST ≥ 3x ULN or confirmed AST ≥ 2 x AST Baseline if AST Baseline > ULN
- Total bilirubin >= 2 x ULN
- Confirmed total bilirubin >= 2 x ULN
- International normalized ratio (INR) > 1.5
- ALT > 3 x ULN at any time during Post-Baseline or AST > 3 x ULN at any time during Post-Baseline
    - And with TBL > 2 x ULN at any time during Post-Baseline
    - And with TBL > 2 x ULN at any time during Post-Baseline and ALP < 2 x ULN at all the time during Post-Baseline, which is Potential Hy's Law

Shift tables from Baseline will be provided using the peak value and the confirmed peak value for ALT, AST, ALP and Bilirubin.

- Categories for ALT and AST will be ≤ULN, >ULN - 3 x ULN, >3 x ULN – 5 x ULN, >5 x ULN – 20 x ULN, and >20 x ULN

- Categories for ALP will be ≤ULN, >ULN - 2.5 x ULN, >2.5 x ULN – 5 x ULN, >5 x ULN – 20 x ULN, and >20 x ULN
- Categories for Bilirubin will be ≤ULN, >ULN - 1.5 x ULN, >1.5 x ULN – 3 x ULN, >3 x ULN – 10 x ULN, and >10 x ULN

For patients that had ALT elevation ≥ 3 x ULN, the time from first dose to first ALT elevation ≥ 3 x ULN will be summarized using the following descriptive statistics: mean, SD, median, P25, P75, and minimum and maximum. Kaplan-Meier plots for time from Day 1 of ION-682884 to first ALT elevation ≥ 3 x ULN will be presented if there are sufficient number of events to make this feasible. Same analyses will be performed for AST.

Shift tables from Baseline for ALT, AST, and total bilirubin based on peak (maximum) and confirmed peak category will also be provided based on CTCAE v5.0. Note, in shift table ALT, AST, and BILI Baseline will be categorized as Normal and Abnormal based on LLN and ULN.

4.12.2.2 Platelets

The number and percentage of patients falling in each of the following categories (using available central and local laboratory assessments) based on post-Baseline assessments will be provided:

- Platelet count - Grade 1a [≥ 100 x 10^9/L to <140 x 10^9/L]
- Platelet count - Grade 1b [≥ 75 x 10^9/L to < 100 x 10^9/L]
- Platelet count - Grade 2 [≥ 50 x 10^9/L to < 75 x 10^9/L]
- Platelet count - Grade 3 [≥ 25 x 10^9/L to < 50 x 10^9/L]
- Platelet count - Grade 4 [< 25 x 10^9/L]
- Platelet count < 140 x 10^9/L
- Platelet count < 100 x 10^9/L
- Platelet count < 75 x 10^9/L
- Platelet count < 50 x 10^9/L
- Platelet count < 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)
- ≥ 30% decrease from Baseline
- ≥ 50% decrease from Baseline
- Confirmed ≥ 30% decrease from Baseline
- Confirmed ≥ 50% decrease from Baseline
- Confirmed platelet count - Grade 1a [≥ 100 x 10^9/L to < 140 x 10^9/L]
- Confirmed platelet count - Grade 1b [≥ 75 x 10^9/L to < 100 x 10^9/L]
- Confirmed platelet count - Grade 2 [≥ 50 x 10^9/L to < 75 x 1^9/L]
- Confirmed platelet count - Grade 3 [≥ 25 x 10^9/L to < 50 x 10^9/L]
- Confirmed platelet count - Grade 4 [< 25 x 10^9/L]
- 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

Furthermore, the platelet counts that define platelet count decrease grades are based on interactions with FDA, and align with the definitions from the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (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 × 10^9/L, ⩾ 100 × 10^9/L to < 140 × 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.

For each of the platelet categories investigated, time from first dose to the onset 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. Kaplan-Meier plots for time to first event will be provided for value < 100 x 10^9/L and value < 140 x1 0^9/L.

Duration of platelet counts below 140 × 10^9/L or 100 x 10^9/L will be summarized, based on the duration (in weeks) each patient was below 140 × 10^9/L or 100 x 10^9/L.

Note that a platelet value of 140 x 10^9/L is the lower limit of normal (LLN) for the central laboratory and will be used as the LLN for all platelet assessments, including those from local labs.

The post-Baseline nadir (absolute value, change from Baseline, and percent change from Baseline) of platelet count will be summarized by treatment group and by Baseline platelet count categories: < 125× 10^9/L, ⩾ 125 to < 150 × 10^9/L, ⩾ 150 to < 175 × 10^9/L, ⩾ 175 to < 200 × 10^9/L, and ≥ 200 × 10^9/L. A listing of subjects in each group that had a nadir platelet count < 75 × 10^9/L (including the corresponding platelet nadir) will also be provided, if applicable.

4.12.2.3 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 will be provided:

- Nadir creatinine clearance by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) >= 90 mL/min/1.73m^2
- Nadir creatinine clearance by CKD-EPI >=60 mL/min/1.73m^2 to < 90 mL/min/1.73m^2
- Nadir creatinine clearance by CKD-EPI >= 30 mL/min/1.73m^2 to < 60 mL/min/1.73m^2
- Nadir creatinine clearance by CKD-EPI >= 15 mL/min/1.73m^2 to < 30 mL/min/1.73m^2
- Nadir creatinine clearance by CKD-EPI < 15 mL/min/1.73m^2
- Creatinine clearance by CKD-EPI ≥ 25% decrease from Baseline
- Creatinine clearance by CKD-EPI ≥ 50% decrease from 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 Baseline
- Confirmed nadir creatinine clearance by CKD-EPI > =90 mL/min/1.73m^2
- Confirmed nadir creatinine clearance by CKD-EPI >=60 mL/min/1.73m^2 to < 90 mL/min/1.73m^2
- Confirmed nadir creatinine clearance by CKD-EPI >= 30 mL/min/1.73m^2 to < 60 mL/min/1.73m^2
- Confirmed nadir creatinine clearance by CKD-EPI >= 15 mL/min/1.73m^2 to < 30 mL/min/1.73m^2
- Confirmed nadir creatinine clearance by CKD-EPI < 15 mL/min/1.73m^2
- Confirmed creatinine clearance by CKD-EPI ≥ 25% decrease from Baseline
- Confirmed creatinine clearance by CKD-EPI ≥ 50% decrease from Baseline
- Confirmed urine Alb/C ratio > 5 x ULN
- Confirmed urine P/C ratio > 5 x ULN
- Confirmed serum creatinine increase > 44.2 umol (0.5 mg/dL) from Baseline
- Urine protein/creatinine ratio (UPCR) > 3 × Baseline and > 1000 mg/g
- UPCR > 5× Baseline AND > 1500 mg/g; or absolute UPCR value ≥ 2000 mg/g
- UPCR > 5 × Baseline and > 1500 mg/g
- UPCR ≥ 2000 mg/g

The eGFR will be used under the equation below:

- CKD-EPI formula (Levey et al. 2009)
  141 x min(Scr/κ, 1)^α × max(Scr/ κ, 1)^(-1.209) × 0.993^Age × 1.018[if female] × 1.159[if black] where Scr is standardized serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

The more recent formulae that do not include a correction factor for race will not be used due to the demographic distribution of the patients in the study (only 4% black/African-American)

Shift tables from ION-682884 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.

If applicable, a listing will be provided for patients who 1) continued treatment with eplontersen after having a UPCR ≥ 1000 mg/g, or 2) continued treatment with eplontersen after having a creatinine clearance by CKD-EPI <= 60 mL/min/1.73m^2.

4.12.3 Vital Signs, Weight, and Physical Findings

Vital signs include systolic and diastolic blood pressure, pulse, respiratory rate, and temperature. Weight will also be analyzed. Absolute values at each visit, change and percent change from Baseline to each visit in vital signs and weight will be summarized by treatment group. No statistical comparisons between treatments will be performed for this summary.

Shift table from Baseline to the highest value and lowest value at any visit will be presented, respectively. The tables will be repeated for the vital signs collected within 24 hours of treatment administration as well.

- Systolic blood pressure: < 90 mmHg, ≥ 90 to ≤ 140 mmHg, > 140 to ≤ 160 mmHg, > 160 mmHg
- Diastolic blood pressure: < 50 mmHg, ≥ 50 to ≤ 90 mmHg, > 90 to ≤ 100 mmHg, > 100 mmHg
- Pulse rate: < 60 bpm, ≥ 60 to ≤ 100 bpm, > 100 bpm

The number and percent of patients meeting any one of the following criteria will be summarized by visit and any visit.

- Body weight: decrease of ≥ 7% from Baseline and increase of ≥ 7% from Baseline
- Temperature: > 38.0 °C, < 36.0 °C
- Respiratory rate: < 12 breaths/min, > 20 breaths/min
- Systolic Blood Pressure: < 90 mmHg, >140 mmHg, > 160 mmHg
- Diastolic Blood Pressure: < 50 mmHg, >90 mmHg, > 100 mmHg
- Pulse Rate: < 60 bpm, > 100 bpm

In addition, the number and percent of patients with treatment-associated abnormal heart rate and blood pressure will be presented. The definition of treatment-associated abnormal heart rate and blood pressure is the measurements within 24 hours of treatment administration and meets the criteria above.

If the “time” of vital sign assessment on the next day is missing, then it will be treated as within 24 hours of treatment administration.

A Listing of treatment-associated abnormal heart rate and blood pressure will be presented.

All test results will be graphed by value (include scheduled and unscheduled visit) for individual patients (spaghetti plots over time) and as aggregate graphs by treatment group (box plot over time).

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

4.12.4 12-Lead Electrocardiograms (12-Lead ECG)

Absolute values, change and percent change from Baseline in ventricular rate and ECG intervals (PR, RR, QRS, QT, QT interval corrected for heart rate [QTc], QTc interval calculated using Bazett's formula [QTcB] and QTc interval calculated using Fridericia’s formula [QTcF]) will be presented by treatment and visit.

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

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

Shift table from Baseline to the worst (highest) post-Baseline value by treatment group will be used to assess the change in the QTcF interval at any visit. 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 with QTcF meeting any one of the following criteria at any post-baseline will be summarized by visit and any visit.

- QTcF >450 msec
- QTcF >480 msec
- QTcF >500 msec
- >30 msec higher than Baseline
- >60 msec higher than Baseline

This analysis will be presented overall and also by the subgroup based on QTcF group (Normal, Abnormal) at 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. No statistical comparisons between treatments will be performed for these summaries.

Ventricular rate and ECG intervals (PR, RR, QRS, QT, QTcB and QTcF), as well as treatment-emergent abnormalities will be listed.

All test results will be graphed by value (include scheduled and unscheduled visit) for individual patients (spaghetti plots over time) and as aggregate graphs by treatment group (box plot over time).

The summaries above will be repeated by CM subgroup and Non-CM subgroup.

The number and percent of patients with QRS>160 ms and >25% above Baseline will be summarized by visit and any visit.

4.12.5 Pregnancy

As applicable, the number and percent female patients with pregnancy during study and outcome of pregnancy will be summarized. As well as summary of all known AEs in patients' offspring.

4.12.6 Ocular Questionnaire

The number and percentage of patients of ocular questionnaire will be summarized by visit and treatment group.

4.12.7 Safety Monitoring (Data and Safety Monitoring Board [DSMB])

DSMB will be assembled and meet periodically to review safety and tolerability data collected on ION-682884 and inotersen, and to review the results of the predetermined interim analysis at Week 35. Based on its assessment of the safety and of ION-682884 and inotersen, the DSMB will provide recommendations to the Sponsor for modifying, stopping or continuing the study as planned.

Details on the safety assessments, frequency of review, meeting schedules and controlled access to data are outlined in the DSMB Charter.

4.13 Determination of Sample Size

The sample size for this study was estimated based on the data from the NEURO-TTR clinical trial.

With 140 patients (120 of them dosed with ION-682884) and assuming a 10% dropout rate, there would be 108 evaluable patients treated with ION-682884. In the NEURO-TTR trial, there are 52 evaluable placebo patients.

It is observed that the NEURO-TTR placebo group had a 23.8 point increase in the mNIS+7 score from Baseline to Week 66. It is estimated that the ION-682884 group will have a 4.2 point increase in mNIS+7. The SD of the change from Baseline is estimated to be 20. There would be at least 90% power to detect a 19.6 point difference in the change from Baseline of the mNIS+7 score between ION-682884-treated patients and the NEURO-TTR-placebo patients, with a 2-sided alpha level of 0.025.

For the Norfolk QOL-DN, it is observed that the NEURO-TTR placebo group had 10.7 points change from Baseline to Week 66. It is estimated that the ION-682884-treated group will have a 0 point change from Baseline. The SD is estimated to be 20. There would be at least 80% power to detect a 10.7 points difference in the change from Baseline of the Norfolk QOL-DN between ION-682884-treated patients and the NEURO-TTR placebo patients, with a 2-sided alpha level of 0.025.

For the TTR percent change from Baseline, it is observed that the NEURO-TTR placebo group had 9.7% reduction from Baseline to Week 65. It is estimated that the ION-682884-treated group will have at least 80% reduction from Baseline. The SD is estimated to be 13%. There would be at least 95% power to detect a 70.3% difference in the percent change from Baseline between ION-682884-treated patients and the NEURO-TTR-placebo patients, with a 2-sided alpha level of 0.025.

4.14 Changes in the Conduct of the Study or Planned Analysis

No changes were made to the planned analyses in the Study Protocol.

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6 Appendix

6.1 Components and Subcomponents of the mNIS+7

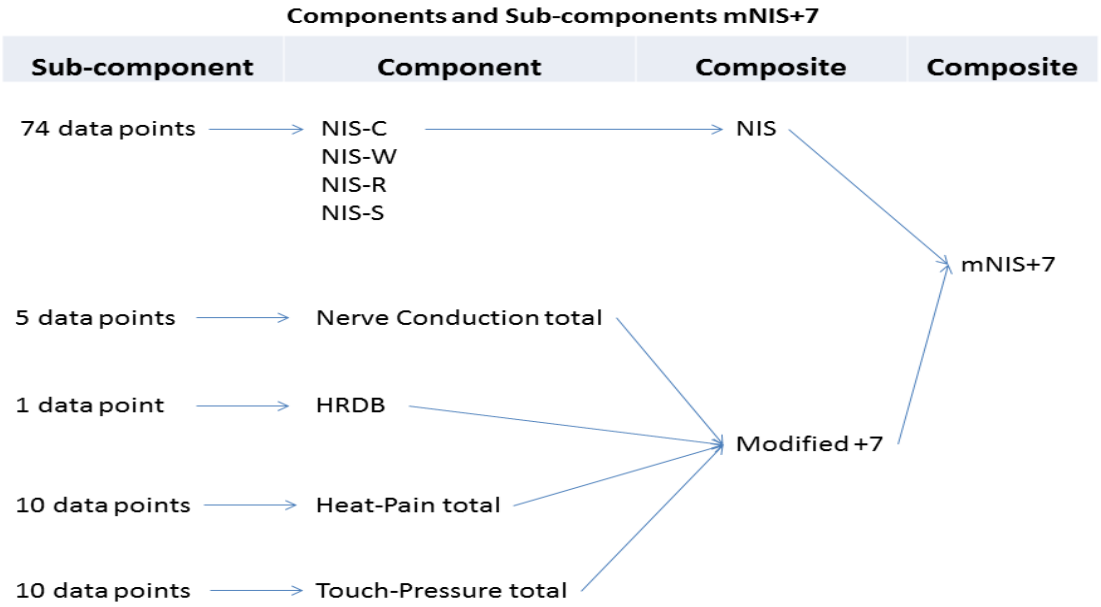

Figure 3 Components and Subcomponents of the mNIS+7

Table 1: Neuropathy Impairment Score

Component	Subcomponent	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		
	24. Toe flexors	0-4	0-4	8	152	
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	20	

Component	Subcomponent	Right Side	Left Side	Max Score	Max Sub-Totals	Missing value imputation for Component Score
	28. Quadriceps femoris	0-2	0-2	4		
	29. triceps surae	0-2	0-2	4		
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	Subcomponent	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 B
Nerve Conduction Tests	Fibular CMAP amplitude (PMAK)	3.72		Group A
	Tibial CMAP amplitude (TMAK)	3.72		
	Ulnar CMAP amplitude (UMAE)	3.72		
	Ulnar SNAP amplitude (USAW)	3.72		
	Sural SNAP amplitude (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		
	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	

Component	Subcomponent	Max Score	Sub-Totals	Missing value imputation for Component Score
Modified +7 Score (Total)			**102.32**	

6.2 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.

6.3 Composite Autonomic Symptom Score (COMPASS-31)

Table 3: COMPASS-31 Scores

Domain	Item	Answer	Points
Orthostatic Intolerance	1	1.Yes	1
		2.No	0
	2	1.Rarely	0
		2.Occasionally	1
		3.Frequently	2
		4.Almost always	3
	3	1.Mild	1
		2.Moderate	2
		3.Severe	3
	4	1.Gotten much worse	3
		2.Gotten somewhat worse	2
		3.Stayed about the same	1
		4.Gotten somewhat better	0
		5.Gotten much better	0
		6.Completely gone	0
Vasomotor	5	1.Yes	1
		2.No	0
	6	1.Hands	1
		2.Feet	1
	7	1.Getting much worse	3
		2.Getting somewhat worse	2
		3.Stayed about the same	1
		4.Getting somewhat better	0
		5.Getting much better	0
		6.Completely gone	0
Secretomotor	8	1.I sweat much more than I used to	1
		2.I sweat somewhat more than I used to	0
		3.I haven’t noticed any change	0
		4.I sweat somewhat less than I used to	1
		5.I sweat much less than I used to	2
	9	1.Yes	1
		2.No	0
	10	1.Yes	1
		2.No	0
	11	1.I have not had any of these symptoms	0
		2.Getting much worse	3
		3.Getting somewhat worse	2
		4.Staying about the same	1
		5.Getting somewhat better	0

Domain	Item	Answer	Points
		6.Getting much better	0
		7.Completely gone	0
Gastrointestinal	12	1.I get full a lot more quickly now than I used to	2
		2.I get full more quickly now than I used to	1
		3.I haven't noticed any change	0
		4.I get full less quickly now than I used to	0
		5.I get full a lot less quickly now than I used to	0
	13	1.Never	0
		2.Sometimes	1
		3.A lot of the time	2
	14	1.Never	0
		2.Sometimes	1
		3.A lot of the time	2
	15	1.Never	0
		2.Sometimes	1
		3.A lot of the time	2
	16	1.Yes	1
		2.No	0
	17	1.Rarely	0
		2.Occasionally	1
		3.Frequently	2
		4.Constantly	3
	18	1.Mild	1
		2.Moderate	2
		3.Severe	3
	19	1.Much worse	3
		2.Somewhat worse	2
		3.Staying the same	1
		4.Somewhat better	0
		5.Much better	0
		6.Completely gone	0
	20	1.Yes	1
		2.No	0
	21	1.Rarely	0
		2.Occasionally	1
		3.Frequently	2
		4.Constantly	3
	22	1.Mild	1
		2.Moderate	2
		3.Severe	3
	23	1.Much worse	3
		2.Somewhat worse	2

Domain	Item	Answer	Points
		3.Staying the same	1
		4.Somewhat better	0
		5.Much better	0
		6.Completely gone	0
Bladder	24	1.Never	0
		2.Occasionally	1
		3.Frequently	2
		4.Constantly	3
	25	1.Never	0
		2.Occasionally	1
		3.Frequently	2
		4.Constantly	3
	26	1.Never	0
		2.Occasionally	1
		3.Frequently	2
		4.Constantly	3
Pupillomotor	27	1.Never	0
		2.Occasionally	1
		3.Frequently	2
		4.Constantly	3
	28	1.Mild	1
		2.Moderate	2
		3.Severe	3
	29	1.Never	0
		2.Occasionally	1
		3.Frequently	2
		4.Constantly	3
	30	1.Mild	1
		2.Moderate	2
		3.Severe	3
	31	1. I have not had any of these symptoms	0
		2.Much worse	3
		3.Somewhat worse	2
		4.Staying the same	1
		5.Somewhat better	0
		6.Much better	0
		7.Completely gone	0

6.4 Sample Programming code for Final Alpha

Below is the sample SAS code for the calculation of the alpha used in the final analysis.

Step 1: obtain the correlation coefficient between interim analysis and final analysis.
Let T1 and T2 be the standardized test statistics at the interim and final analyses, respectively. In order to determine the alpha level for the final analysis, the correlation between T1 and T2 is first estimated based on the resampling approach:

- Among the 108 ION-682884-treated patients and 52 NEURO-TTR placebo patients, randomly assign 108 patients to the ION-682884 treated group and 52 patients to NEURO-TTR placebo group
- Apply the re-randomized treatment assignment to the interim data and obtain the standardized test statistics T1
- Apply the re-randomized treatment assignment to the final data and obtain the standardized test statistics T2
- Repeat the above procedure N times (N = 10000) and obtain N pairs of test statistics T1 and T2.
- A random seed of 2855 will be used to generate N times resampling.

```
%macro simulation(seed=xx);
%do i=1 %to 10000;
data adsl;
 set adsl;
 x=ranuni(%eval(&seed+&i));
run;

proc sort;  by x; run;

data adsl;
 set adsl;
 by x;
 if _n_<=52 then treatment=1;
 else treatment=2;
run;

data Interim&i;
 merge InterimData adsl;
 by subject_id;
 trial=&i;
run;

data Final&i;
 merge FinalData adsl;
 by subject_id;
 trial=&i;
run;

%end;

data Interim;
 set %do i=1 %to 10000; Interim&i %end;;
run;

data Final;
 set %do i=1 %to 10000; Final&i %end;;
run;
```

```
%mend;

%simulation(seed=nn);
ods output diffs=diff35(rename=(tvalue=t35);
PROC MIXED DATA=interim;
 By trial;
 CLASS treatment visit subject_id PRETRTI DISTAI V30TTRI;
 MODEL endpoint=treatment baseline PRETRTI DISTAI V30TTRI visit visit*baseline visit*treatment / DDFM=kr;
 REPEATED visit / SUBJECT=subject_id TYPE=un;
 LSMEANS visit*treatment / CL DIFF=control("1" "35");
 Weight wt;
RUN;

ods output diffs=diff66(rename=(tvalue=t66);
PROC MIXED DATA=Final;
 By trial;
 CLASS treatment visit subject_id PRETRTI DISTAI V30TTRI;
 MODEL endpoint=treatment baseline PRETRTI DISTAI V30TTRI visit visit*baseline visit*treatment / DDFM=kr;
 REPEATED visit / SUBJECT=subject_id TYPE=un;
 LSMEANS visit*treatment / CL DIFF=control("1" "66");
 Weight wt;
RUN;
data diff;
 merge diff35 diff66;
  by trial;
run;
```

The correlation between T1 and T2 will then be estimated as the sample correlation of the N pairs.

```
proc corr;
 var t35 t66;
run;
```

Step 2: Below is the sample SAS code for the calculation of the alpha used in the final analysis. In this example, the correlation coefficient (r) between T1 and T2 is assumed to be 0.636, and two-side alpha 0.025 is used for interim analysis. Overall alpha is 0.05. The following SAS code will create the final two-sided alpha to be used.

```
proc fcmp;
   function totalalpha(corr, ts1, ts2);
      p1=cdf('NORMAL',ts1); /*probability for T1 up to ts1 (interim analysis), T2 up
to infinity.  This is marginal prob in the interim analysis. */
      p2=cdf('NORMAL',ts2); /*probability for T1 up to infinity, T2 up to ts2.*/
      p3=probbnrm(ts1,ts2,corr); /*joint probability for T1 up to ts1 (interim
analysis), T2 up to ts2 . */
      return(2*(p1+p2-p3)-0.05);
   endsub;

   array opts[5] initial abconv relconv maxiter status (0 1.0e-12 1.0e-6 1000 -1);

   corr=0.636;
   ts1=quantile('NORMAL',0.025/2);
   ts2=solve("totalalpha", opts, 0, corr, ts1, .); /*this is the two-side alpha for
the final analysis.*/

   /* result */
   ts1p=cdf('NORMAL',ts1);
   ts2p=cdf('NORMAL',ts2);
   p1=cdf('NORMAL',ts1);
```

```
   p2=cdf('NORMAL',ts2);
   p3=probbnrm(ts1,ts2,corr);
   totalalpha=(p1+p2-p3)*2;
   final=p2*2;
   put "cor =" corr;
   put "ts1 =" ts1 "; ts1 prob =" ts1p;
   put "ts2 =" ts2 "; ts2 prob =" ts2p;
   put "total alpha =" totalalpha;
   put "alpha level for final analysis =" final;

run;
```

6.5 Laboratory Parameters' Classification by CTCAE v5.0

Selected Laboratory Parameters' Classification by CTCAE v5.0. Of note, grade 0 was added to present normal lab value.

Chemistry Lab Tests

Creatine kinase

Grade 0: ≤ ULN, Grade 1: > ULN – 2.5 x ULN, Grade 2: > 2.5 – 5.0 x ULN, Grade 3: > 5.0 – 10.0 x ULN, Grade 4: > 10.0 x ULN.

The worst value should be the peak value.

Serum creatinine

Grade 0: ≤ ULN, Grade 1: > ULN – 1.5 x ULN, Grade 2: > 1.5 – 3.0 x ULN or > 1.5 - 3.0 x baseline, Grade 3: > 3.0 – 6.0 x ULN or > 3.0 x baseline, Grade 4: > 6.0 x ULN.

The worst value should be the peak value.

Calcium (increased) (mmol/L)

Grade 0: corrected serum calcium of ≤ ULN, Grade 1: corrected serum calcium of > ULN – 2.9 mmol/L, Grade 2: corrected serum calcium of > 2.9 – 3.1 x mmol/L, Grade 3: corrected serum calcium of > 3.1 – 3.4 mmol/L, Grade 4: > 3.4 mmol/L.

The worst value should be the peak value.

Calcium (decreased) (mmol/L)

Grade 0: corrected serum calcium of ≥ LLN, Grade 1: corrected serum calcium of < LLN – 2.0 mmol/L, Grade 2: corrected serum calcium of < 2.0 – 1.75 mmol/L, Grade 3: corrected serum calcium of < 1.75 – 1.5 mmol/L, Grade 4: corrected serum calcium of < 1.5 mmol/L.

The worst value should be the nadir value.

Glucose (decreased) (mmol/L)

Grade 0: fasting glucose value ≥ LLN, Grade 1: fasting glucose value < LLN – 3.0 mmol/L, Grade 2: fasting glucose value < 3.0 – 2.2 mmol/L, Grade 3: fasting glucose value < 2.2 – 1.7 mmol/L, Grade 4: fasting glucose value <1.7 mmol/L.

The worst value should be the nadir value.

Potassium (increased) (mmol/L)

Grade 0: ≤ ULN, Grade 1: > ULN – 5.5 mmol/L, Grade 2: > 5.5 – 6.0 mmol/L, Grade 3: > 6.0 – 7.0 mmol/L, Grade 4: > 7.0 mmol/L.

The worst value should be the peak value.

Potassium (decreased) (mmol/L)

Grade 0: ≥ LLN, Grade 1: < LLN – 3.0 mmol/L, Grade 2: Symptomatic with < LLN – 3.0 mmol/L intervention indicated, Grade 3: < 3.0 – 2.5 mmol/L, Grade 4: <2.5 mmol/L.

The worst value should be the nadir value. Note, since grade 1 and grade 2 has same numerical criteria, go with grade 2.

Magnesium (increased) (mmol/L)

Grade 0: ≤ ULN, Grade 1: > ULN – 1.23 mmol/L, Grade 2: -, Grade 3: > 1.23 – 3.30 mmol/L, Grade 4: > 3.30 mmol/L.

The worst value should be the peak value.

Magnesium (decreased) (mmol/L)

Grade 0: ≥ LLN, Grade 1: < LLN – 0.5 mmol/L, Grade 2: < 0.5 – 0.4 mmol/L, Grade 3: < 0.4 – 0.3 mmol/L, Grade 4: <0.3 mmol/L.

The worst value should be the nadir value.

Sodium (increased) (mmol/L)

Grade 0: ≤ ULN, Grade 1: > ULN – 150 mmol/L, Grade 2: > 150 – 155 mmol/L, Grade 3: > 155 – 160 mmol/L, Grade 4: > 160 mmol/L.

The worst value should be the peak value.

Sodium (decreased) (mmol/L)

Grade 0: ≥ LLN, Grade 1: < LLN – 130 mmol/L, Grade 2: 125-129 mmol/L and asymptomatic, Grade 3: 125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms, Grade 4: < 120 mmol/L.

The worst value should be the nadir value. Note, grade 3 and grade 2 has same numerical criteria. Go with Grade 3

Albumin (decreased) (g/L)

Grade 0: ≥ LLN, Grade 1: < LLN – 30 g/L, Grade 2: < 30 – 20 g/L, Grade 3: <20 g/L.

The worst value should be the nadir value.

Haematology Lab Tests

Hemoglobin (increased) (g/L)

Grade 0:Increase <=0, Grade 1: Increase in >0 - 20 g/L, Grade 2: Increase in >20 - 40 g/L, Grade 3: Increase in >40 g/L.

The worst value should be the peak value.

Hemoglobin (decreased) (g/L)

Grade 0: Hemoglobin (Hgb)≥ LLN, Grade 1: < LLN – 100 g/L, Grade 2: < 100 – 80 g/L, Grade 3: < 80 g/L.

The worst value should be the nadir value.

Lymphocyte count (increased) (10^9/L)

Grade 0: <=4 x 10^9, Grade 2: > 4 x 10^9/L – 20 x 10^9/L, Grade 3: > 20 x 10^9/L.

The worst value should be the peak value.

Lymphocyte count (decreased) (10^9/L)

Grade 0: ≥ LLN, Grade 1: < LLN – 0.8 x 10^9/L, Grade 2: < 0.8 – 0.5 x 10^9/L, Grade 3: < 0.5 - 0.2 x 10^9/L, Grade 4: < 0.2 x 10^9/L.

The worst value should be the nadir value.

Neutrophil count decreased (10^9/L)

Grade 0: ≥ 1.8 x 10^9/L, Grade 1: < 1.8 – 1.5 x 10^9/L, Grade 2: < 1.5 – 1.0 x 10^9/L, Grade 3: < 1.0 - 0.5 x 10^9/L, Grade 4: < 0.5 x 10^9/L.

The worst value should be the nadir value. Note, grade 1 was modified from CTCAT v5.0

WBC (increased) (10^9/L)

Grade 0: Grade 0 is <=100 x 10^9/L , Grade 3: > 100 x 10^9/L.

The worst value should be the peak value.

WBC (decreased) (10^9/L)

Grade 0: ⩾ LLN, Grade 1: < LLN – 3.0 x 10^9/L, Grade 2: < 3.0 – 2.0 x 10^9/L, Grade 3: < 2.0 – 1.0 x 10^9/L, Grade 4: < 1.0 x 10^9/L.

The worst value should be the nadir value

Coagulation Lab Tests

aPTT (Unit)

Grade 0: ⩽ ULN, Grade 1: > ULN – 1.5 x ULN, Grade 2: > 1.5 – 2.5 x ULN, Grade 3: > 2.5 x ULN ; bleeding.

The worst value should be the peak value.

INR (Unit)
Grade 0: <=1.2, Grade 1: >1.2 – 1.5, Grade 2: > 1.5 – 2.5, Grade 3: > 2.5 ;

The worst value should be the peak value.

6.6 List of Changes in the Statistical Analysis Plan

List of Changes in Version 2.1

SAP Section(s) Impacted	Description of Modification
Overall	Updated document version to 2.1 to correct section numbering throughout SAP
1	Updated to current versions of protocols used.
2.4.1	Updated efficacy objectives: To evaluate the efficacy of ION-682884 in the Change from Baseline in the Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) at Weeks 37 and 85. To evaluate the efficacy of ION-682884, as compared to the historical control of the placebo arm included in the ALN-TTR02-004 (APOLLO trial, ClinicalTrials.gov Identifier: NCT01960348) in the following measures at Week 85.
4.1.7	Updated SF-36 version to Quality Metric PRO CoRE Smart Measurement System, PRO CoRE Version 2.1.
4.1.8	Updated MedDRA version to 25.0 or later and WHODRUG to Mar2022 or later.
Update as 4.2.1.1	Added: Baseline ECG will be defined as the value taken on Day 1 pre-dose. If the triplicates are taken, the average of the triplicates will be used.
4.2.1.2	ION-682884 baseline will be defined as the last non-missing assessment prior to the first dose of ION-682884.
4.2.3	Updated Analysis Visit Windows for Serum TTR.
4.5.4	Added: PPS will be defined separately for interim analysis at Week 35 and final analysis at Week 66.
4.6	Added serum TTR and High-Sensitivity Troponin T in the summary part.
4.6	Added the genotyping category: The TTR genotype category will be summarized by V30M vs. Non-V30M. The V30M genotype category includes V30M Mutation ('Yes') and VAL50MET, V50M MUTATION, V50M and P.VAL50MET listed under the "Other" category in CRF.
4.9	Added: Duration of drug exposure (month) and total amount of ION-682884 administered (mg) will be summarized by baseline platelet count categories $< 125 \times 10^9$/L, ≥ 125 to $< 150 \times 10^9$/L, ≥ 150 to $< 175 \times 10^9$/L, ≥ 175 to $< 200 \times 10^9$/L, and $\geq 200 \times 10^9$/L.
4.10.1	Reference to ELISA assay corrected to ECL assay

SAP Section(s) Impacted	Description of Modification
4.10.2.1	For primary analysis using MMRM, added additional options in case there are convergence issues.
4.10.3.1	Specify Sensitivity Analysis 2 to 4 apply to which endpoint at interim and final analysis: These sensitivity analyses will be applied for serum TTR in the Week 35 interim analysis and serum TTR, mNIS+7, and Norfolk in Week 66 final analyses.
4.10.3.1	Added the Sensitivity Analysis 6 for Norfolk.
4.10.3.1	Added Sensitivity Analysis 8 (Observed data) for mNIS+7 and Norfolk at week 35 interim analysis.
4.10.4	Added the ANCOVA model for mNIS+7 and Norfolk at week 35 interim analysis. Added subgroups of FAC Clinical Diagnosis from CRF and CM subgroup.
4.10.7	Added analysis for log-transformed NT-proBNP and Troponin T
4.11.3.3	Added: Lastly, other stratifications (e.g., based on antibody titer, onset of ADA, subjects with treatment-emergent ADA vs. treatment-unaffected ADA etc.)
4.12.1	Added imputation rule for partial missing date in adverse event
4.12.1	Added CM subgroup for analysis.
4.12.1	Added AE summary table for incidence rate and event rate per 100 patient years of exposure.
4.12.1.1	Updated the definition of AESI and other AE of special interest.
4.12.1.3	Added a section for local cutaneous reactions at injection site (LCRIS) and Injection site reaction: - Injection Site Reaction (ISR) defined as TEAEs with MedDRA preferred terms contains text “Injection site”. ISR will be summarized by SOC and PT. In addition, ISR will be summarized by SOC, PT and injection location which is the location of the last injection prior to AE onset. - The following MedDRA preferred terms are determined by the Sponsor’s Pharmacovigilance personnel to represent the Local Cutaneous Reactions at Injection Site (LCRIS): • Injection site erythema • Injection site swelling • Injection site pruritus • Injection site pain • Injection site tenderness 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

SAP Section(s) Impacted	Description of Modification
	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.
4.12.1.4	Added a section for 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: 1. Chills 2. Myalgia 3. Arthralgia
4.12.1.5	Added TEAE related renal safety.
4.12.2 Appendix 6.5	Added CTCAE v5.0
4.12.2.1	Added: ALT, AST, ALP and Bilirubin category criteria for shift table. • Categories for ALT and AST will be ≤ULN, >ULN - 3 x ULN, >3 x ULN – 5 x ULN, >5 x ULN – 20 x ULN, and >20 x ULN • Categories for ALP will be ≤ULN, >ULN - 2.5 x ULN, >2.5 x ULN – 5 x ULN, >5 x ULN – 20 x ULN, and >20 x ULN • Categories for Bilirubin will be ≤ULN, >ULN – 1.5 x ULN, >1.5 x ULN – 3 x ULN, >3 x ULN – 10 x ULN, and >10 x ULN
4.12.2.2	Added platelet summary table by baseline platelet category.
4.12.2.3	Added: Shift tables from ION-682884 baseline for creatinine clearance by CKD-EPI will be provided using the nadir value and the confirmed nadir category.
4.12.3	Added vital signs shift tables, and add vital signs summary table based on data collected within 24 hours of treatment administration.
4.12.4	Added: The number and percent of patients with QTcF meeting any one of the following criteria at any post-baseline will be summarized by visit and any visit. • QTcF >450 msec • QTcF >480 msec • QTcF >500 msec • >30 msec higher than Baseline • >60 msec higher than Baseline
4.12.5	Added Section 4.12.5 Pregnancy

SAP Section(s) Impacted	Description of Modification
4.12.6	Removed shift tables from Baseline in ocular questionnaire will be also summarized by visit and treatment group.