IONIS PHARMACEUTICALS, INC.

ISIS 420915-CS2

A Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy

Protocol Amendment 9 – 13 May 2016

EudraCT No: 2012-001831-30

Sponsor:

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

ISIS 420915-CS2

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Protocol History:

Original Protocol:	21 September 2012
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Amendment 8:	7 March 2016

Sponsor:

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PPD

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PPD , PPD

ISIS 420915

Ionis Protocol Number ISIS 420915-CS2

Protocol Amendment 9

EudraCT No: 2012-001831-30

Clinical Phase: 2/3

A Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy

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Date: 13 May 2016

Confidentiality Statement

Protocol Signature Page

Protocol Number: ISIS 420915-CS2

Protocol Title: A Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy

Amendment: Amendment 9

Date: 13 May 2016

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "A Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy", dated 13 May 2016, and agree to conduct the study as described herein.

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

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

Investigator's Signature

Investigator's Name *(please print)*

Date (DD Month YYYY)

TABLE OF CONTENTS

Page

TABLE OF TABLES

Page

TABLE OF FIGURES

Page

PROTOCOL AMENDMENT

Protocol Number: ISIS 420915-CS2

Protocol Title: A Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy

Amendment Number: 9

Amendment Date: 13 May 2016

The main purpose of this amendment is to increase the frequency of platelet monitoring from every 2-3 weeks, to every week throughout the treatment period and for a minimum of 6 weeks after the last dose of Study Drug. This change was made in response to a recently reported case of severe thrombocytopenia in this study and in consultation with the independent DSMB. Previous to this recent case, two other patients in this study have developed severe thrombocytopenia, one of whom experienced a fatal intracranial bleed.

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

The following table provides a summary list of major changes to the protocol:

Protocol Section	Description of Change	Rationale
3.4.3 Post-Treatment	Was: The post-treatment evaluation period is 6 months and consists of 3 Study Center visits on Weeks 71, 77 and 91. The final study visit is Week 91. Is: The post-treatment evaluation period is 6 months and consists of Study Center visits **and additional safety testing.** The final study visit is Week 91.	Language with regard to the visit schedule and laboratory safety testing has been updated to reflect the new schedule of procedures.
6.1.2 Treatment Period	Was: Patients will report to the Study Center for Study Drug administration, evaluations, and tests 24 times during Weeks 2-65 (see Schedule of Procedures in Appendix A). Is: Patients will report to the Study Center for Study Drug administration, evaluations, and tests **regularly throughout the treatment period and will have weekly safety testing according to the** schedule of procedures in Appendix A.	Language with regard to the visit schedule and laboratory safety testing has been updated to reflect the new schedule of procedures.

Protocol Section	Description of Change	Rationale
6.1.2 Treatment Period *Continued*	Was: To help reduce patient travel burden, 13 clinic visits may be done as non-clinic visits during the treatment period. For non-clinic visits, collection of vital signs and labs (as indicated in the Schedule of Procedures) can be performed by the Sponsor's home healthcare service or by a local laboratory with prior Sponsor approval. The selected visits are at Weeks 10, 15, 20, 23, 26, 32, 38, 41, 44, 50, 56, 59, and 62. At Weeks 23, 41 and 59, adverse events should be collected by the site personal through a phone contact with the patient. Is: To help reduce patient travel burden, **some clinic visits and weekly safety testing between** visits may be done as non-clinic visits. For non-clinic visits, collection of vital signs and labs (as indicated in the Schedule of Procedures) can be performed by the Sponsor's home healthcare service or by a local laboratory with prior Sponsor approval.	Language with regard to the visit schedule and laboratory safety testing has been updated to reflect the new schedule of procedures.
6.1.4 Post-Treatment Period	Was: After completion of the EOT efficacy assessment, patients will enter the 6-month post-treatment evaluation period. This period consists of 8 Study Center visits on Weeks 67, 69, 71, 74, 77, 80, 83, and 91 as outlined in the schedule of procedures (Appendix A). Weeks 67, 69, 71, 74, 80 and 83 may be done as a non-clinic visit where collection of vital signs and labs may be collected by the Sponsor's home healthcare service or by a local laboratory with prior Sponsor approval. At Week 71, adverse events should be collected by the site personal through a phone contact with the patient. Alternatively, after completion of the EOT efficacy assessment, eligible patients may elect to receive ISIS 420915 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. Is: After completion of the EOT efficacy assessment, patients will enter the 6-month post-treatment evaluation period **and will report to the study center and have weekly platelet monitoring for a minimum of 6 weeks after the last dose of Study Drug which may be collected by the clinic, Sponsor's home healthcare service or by a local laboratory** as outlined in the schedule of procedures (Appendix A). At Week 71, adverse events should be collected by the site personal through a phone contact with the patient **if a clinic visit was not conducted.**	Language with regard to the visit schedule and laboratory safety testing has been updated to reflect the new schedule of procedures.

Protocol Section	Description of Change	Rationale
6.1.4 Post-Treatment Period *Continued*	Is: *Continued* Alternatively, after completion of the EOT efficacy assessment, eligible patients may elect to receive ISIS 420915 in an OLE study **(ISIS 420915-CS3)**, 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 **but weekly platelet monitoring should continue between the last dose of Study Drug in CS2 and the first dose of Study Drug in CS3. If this period extends beyond 6 weeks, the frequency will be determined by the Study Medical Monitor.**	Language with regard to the visit schedule and laboratory safety testing has been updated to reflect the new schedule of procedures.
6.2.1 Laboratory Assessments	Deleted: Each time a hematology lab is collected a duplicate sample (e.g., local lab) should also be collected in parallel. If both the central and local platelet value is uninterpretable (e.g., due to clumping, hemolysis or quantity not sufficient) a repeat hematology lab must be collected as soon as possible (within 7 days after the unreportable value).	Because platelet counts will be monitored more frequently, the requirement to collect a local lab sample at the same time as the samples for the central lab has been removed.
8.5.4 Safety Monitoring Rules for Platelet Count Results	Was: If a patient's platelet count falls by 30% or greater from baseline or the absolute platelet count is 100,000/mm^3 or less, then the patient's platelet counts should be monitored more frequently. The frequency of monitoring and additional lab tests will be determined by the Investigator in consultation with the Study Medical Monitor. Additional details on monitoring platelets are described in the Safety Management Plan. Is: **Platelets will be monitored weekly throughout the treatment period and for a minimum of 6 weeks after the last dose of Study Drug (this includes early termination patients as well as patients that complete the full 65-week treatment period). For patients participating in the Post-Treatment Evaluation Period, frequency of testing after the Week 71 visit will be determined by the Investigator in consultation with the Study Medical Monitor. For patients participating in the ISIS 420915-CS3 study, weekly monitoring should continue between the last dose of Study Drug in CS2 and first dose of Study Drug in CS3. If this period extends beyond 6 weeks, the frequency of monitoring will be determined by the Study Medical Monitor.** **All platelet count results must be promptly reviewed by the Investigator to ensure that the count has not met the stopping rule.**	The monitoring rule has been updated to reflect the weekly platelet monitoring and to indicate that dosing must be held if there is more than 14 days between interpretable platelet values.

Protocol Section	Description of Change	Rationale
8.5.4 Safety Monitoring Rules for Platelet Count Results *Continued*	Is: *Continued* **If, for any reason, there is more than 14 days between platelet values (e.g., lab report of an unreadable sample due to clumping, hemolysis, or quantity not sufficient, or a missed lab assessment), the Investigator will contact the patient to hold dosing until a new platelet value is obtained and reviewed.** **If a patient's platelet counts fall below 100,000/mm^3, additional lab tests may be requested as determined by the Investigator in consultation with the Study Medical Monitor.**	The monitoring rule has been updated to reflect the weekly platelet monitoring and to indicate that dosing must be held if there is more than 14 days between interpretable platelet values.
8.6.3 Stopping Rule for Platelet Count Results	Was: In the event of a confirmed platelet count less than 75,000/mm^3, and in the absence of major bleeding or clinically-relevant non-major bleeding, further dosing of a patient with Study Drug (ISIS 420915 or placebo) must be held until the platelet count returns to at least 100,000/mm^3. In addition, platelet counts should be monitored weekly (or more frequently as determined by the Study Medical Monitor) until they return above 75,000/mm^3. Is: In the event of a confirmed platelet count less than 75,000/mm^3, and in the absence of major bleeding or clinically-relevant non-major bleeding, further dosing of a patient with Study Drug (ISIS 420915 or placebo) must be held until the platelet count returns to at least 100,000/mm^3. **Weekly platelet monitoring should continue during this period. In addition, the Investigator should give consideration to collecting duplicate platelet samples for study in a local lab in parallel to the central lab if it would provide quicker access to the patients platelet count. If the platelet count was confirmed to be < 50,000/mm^3, then monitoring should be increased to daily until two successive values show improvement. The Investigator must notify the Study Medical Monitor within 24 hours of any local lab platelet results that show a level < 50,000/mm^3.**	Platelet stopping rule has been updated to indicate daily platelet monitoring is required if the platelet value is < 50,000/mm^3 and that the Investigator is required to inform the Study Medical Monitor within 24 hours if a local platelet value is < 50,000/mm^3.
Appendix A Schedule of Procedures	Deleted: To accommodate scheduling, visit windows may be used, however hematology collections must be collected no more than 2-3 weeks apart. + Each time a hematology lab is collected a duplicate sample (e.g., local lab) should also be collected in parallel. If both the central and local platelet value is uninterpretable (e.g., due to clumping, hemolysis or quantity not sufficient) a repeat hematology lab must be collected as soon as possible (within 7 days after the unreportable value).	The schedule of procedures was updated to reflect the weekly platelet monitoring and removal of duplicate platelet collection.

Protocol Section	Description of Change	Rationale
Appendix A Schedule of Procedures *Continued*	Added: Weekly platelet monitoring was added throughout the treatment period and up to Week 71 in the post-treatment evaluation period. Footnote to weekly platelet monitoring added: Weekly platelet monitoring is required throughout the treatment period and for a minimum of 6 weeks after the last dose of Study Drug (this includes early termination patients as well as patients that complete the full 65-week treatment period). For patients participating in the Post-Treatment Evaluation Period, frequency of testing after the Week 71 visit will be determined by the Study Medical Monitor in consultation with the Investigator. For patients participating in the ISIS 420915-CS3 study, weekly monitoring should continue between the last dose of Study Drug in CS2 and first dose of Study Drug in CS3. If this period extends beyond 6 weeks, the frequency will be determined by the Study Medical Monitor. The following visits to collect platelet values are required in addition to the visits shown in the table. These visits do not have specified windows to allow flexibility of scheduling but with the intent that platelets are assessed each calendar week. Visits may be completed in clinic, by home healthcare service, or by a local laboratory: Week 2, 4, 6, 7, 9, 11, 12, 14, 16, 17, 19, 21, 22, 24, 25, 27, 28, 30, 31, 33, 34, 36, 37, 39, 40, 42, 43, 45, 46, 48, 49, 51, 52, 54, 55, 57, 58, 60, 61, 63, 64, 66, 68, and 70	The schedule of procedures was updated to reflect the weekly platelet monitoring and removal of duplicate platelet collection.
Appendix B List of Laboratory Analytes	Added: Total IgG Total IgM	Added two new laboratory analytes.

PROTOCOL SYNOPSIS

Protocol Title	A Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy (FAP)
Study Phase	Phase 2/3
Indication	Familial Amyloid Polyneuropathy
Primary Objectives	To evaluate the efficacy of ISIS 420915 as compared to placebo, given for 65 weeks, as measured by the change from baseline in the modified Neuropathy Impairment Score +7 (mNIS+7) and in the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) questionnaire total score, in patients with FAP
Secondary Objectives	To evaluate the efficacy of ISIS 420915 as compared to placebo, based on the change from baseline in the following measures: 1. Norfolk QOL-DN questionnaire symptoms domain score in Stage 1 patients and Norfolk QOL-DN questionnaire physical functioning/large fiber neuropathy domain score in Stage 2 patients 2. Modified body mass index (mBMI) and body mass index (BMI) 3. NIS and modified +7 4. NIS+7 5. Global longitudinal strain (GLS) by echocardiogram (ECHO) in the ECHO subgroup and in the Cardiomyopathy-ECHO (CM-ECHO) Set To evaluate the pharmacodynamic (PD) effect of ISIS 420915 as compared to placebo, based on the change from baseline in transthyretin (TTR) and retinol binding protein 4 (RBP4). To evaluate the safety and tolerability of ISIS 420915. To evaluate the plasma trough levels of ISIS 420915 in all patients and to evaluate the plasma pharmacokinetic parameters of ISIS 420915 in a subset of patients.
Tertiary Objectives	To evaluate the change from baseline as compared to placebo in the following measures: • SF-36 questionnaire • Individual components of NIS, modified +7, and +7 • +7 • Individual domain scores of the Norfolk QOL-DN questionnaire
Exploratory Objectives	To evaluate the change from baseline as compared to placebo in the following exploratory measures: • ECHO parameters (except GLS) in the ECHO subgroup and in the CM-ECHO Set • Plasma N-terminal prohormone of brain natriuretic peptide (NT-proBNP) • Polyneuropathy disability score (PND) • Neuropathy symptoms and change (NSC) score

Protocol Synopsis *Continued*

Study Design	Multicentre, randomized, double-blind, placebo-controlled study. Approximately 135 patients will be randomized in a 2:1 ratio (90 ISIS 420915 and 45 PBO) to receive 300 mg ISIS 420915 or placebo. Study Drug (ISIS 420915 or placebo) will be administered 3 times on alternate days during Week 1 (Days 1, 3 and 5), and then once weekly during Weeks 2-65 (for a total of 67 doses). Patients will also receive daily supplemental doses of the recommended daily allowance of vitamin A. The end of treatment (EOT) efficacy assessment is conducted at Week 66. Following treatment and the EOT efficacy assessment, eligible patients (including patients that received placebo), may elect to enroll in an open-label extension (OLE) study pending study approval by the IRB/IEC and the appropriate regulatory authority. All participating patients in the OLE study will receive 300 mg ISIS 420915 once weekly. Patients not participating in the OLE will enter the 6-month post-treatment evaluation portion of this study after completing the EOT efficacy assessment.
Number of Patients	Approximately 135 patients will be enrolled into this study
Study Population	Inclusion Criteria: 1. Stage 1 and Stage 2 FAP patients with the following: a. NIS score ≥ 10 and ≤ 130 b. Documented transthyretin variant by genotyping c. Documented amyloid deposit by biopsy 2. Willingness to take vitamin A supplements 3. Aged 18 to 82 years old at the time of informed consent 4. Satisfy the following: a. Females: non-pregnant and non-lactating; surgically sterile, post-menopausal, abstinent, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 3 months after the last dose of Study Drug b. Males: Surgically sterile, abstinent, or if engaged in sexual relations of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) during and for 3 months after the last dose of Study Drug 5. 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 Exclusion Criteria: 1. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator 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. ALT/AST > 1.9 x ULN b. Bilirubin ≥ 1.5 x ULN (patients with bilirubin ≥ 1.5 x ULN may be allowed on study following discussion with the Study Medical Monitor if indirect bilirubin only is elevated, ALT/AST is not greater than the ULN and genetic testing confirming Gilbert's disease) c. Platelets < 125 x 10^9/L d. Positive (≥ trace) for protein on urine dipstick. In the event of a positive test eligibility may be confirmed by a quantitative total urine protein measurement of < 1.0 g/24 hours

Protocol Synopsis *Continued*

Study Population *Continued*	Exclusion Criteria: *Continued* e. Positive (≥ trace) for blood on urine dipstick. In the event of a positive test eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field. If > 5 red blood cells per high power field and there is a clearly identifiable benign cause for the microscopic hematuria (for example chronic urinary tract infection secondary to neurogenic bladder) eligibility should be determined by discussion with the Study Medical Monitor f. TSH values outside normal range (unless approved by the Study Medical Monitor) 3. Retinol level at Screen < LLN • For patients with a TTR mutation at position 84 (e.g., Ile84Ser or Ile84Asn) and retinol < LLN the exclusion criterion is signs or symptoms of vitamin A deficiency (such as evidence of vitamin A deficiency on ERG) 4. Uncontrolled hypertension (blood pressure > 160/100) 5. Positive test result for HIV, hepatitis B, or hepatitis C 6. Karnofsky performance status ≤ 50 7. Renal insufficiency as defined by estimated creatinine clearance calculated according to the formula of CKD-EPI < 60 mL/min/1.73 m^2 at Screen. If the calculated creatinine clearance is thought to be artificially low, a 24-hour urine creatinine clearance can be completed with prior Sponsor approval 8. Presence of known type 1 or type 2 diabetes mellitus 9. Other causes of sensorimotor or autonomic neuropathy (e.g., autoimmune disease) 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. If previously treated with Vyndaqel®, must have discontinued treatment for 2 weeks prior to Study Day 1. If previously treated with Diflunisal, must have discontinued treatment for 3 days prior to Study Day 1 12. Previous treatment with any oligonucleotide or siRNA within 6 months of Screening. Subjects that have been previously treated with oligonucleotides should be approved by the Study Medical Monitor 13. Prior liver transplant or anticipated liver transplant within 1-yr of Screening 14. New York Heart Association (NYHA) functional classification of ≥ 3 15. Acute coronary syndrome or major surgery within 3 months of Screening 16. Known Primary Amyloidosis 17. Known Leptomeningeal Amyloidosis 18. Anticipated survival less than 2 years 19. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1 20. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated. Patients with a history of other malignancies that have been curatively treated may be eligible but must be discussed and approved by the Sponsor Medical Monitor 21. 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 22. Known Monoclonal Gammopathy of Undetermined Significance or Multiple Myeloma

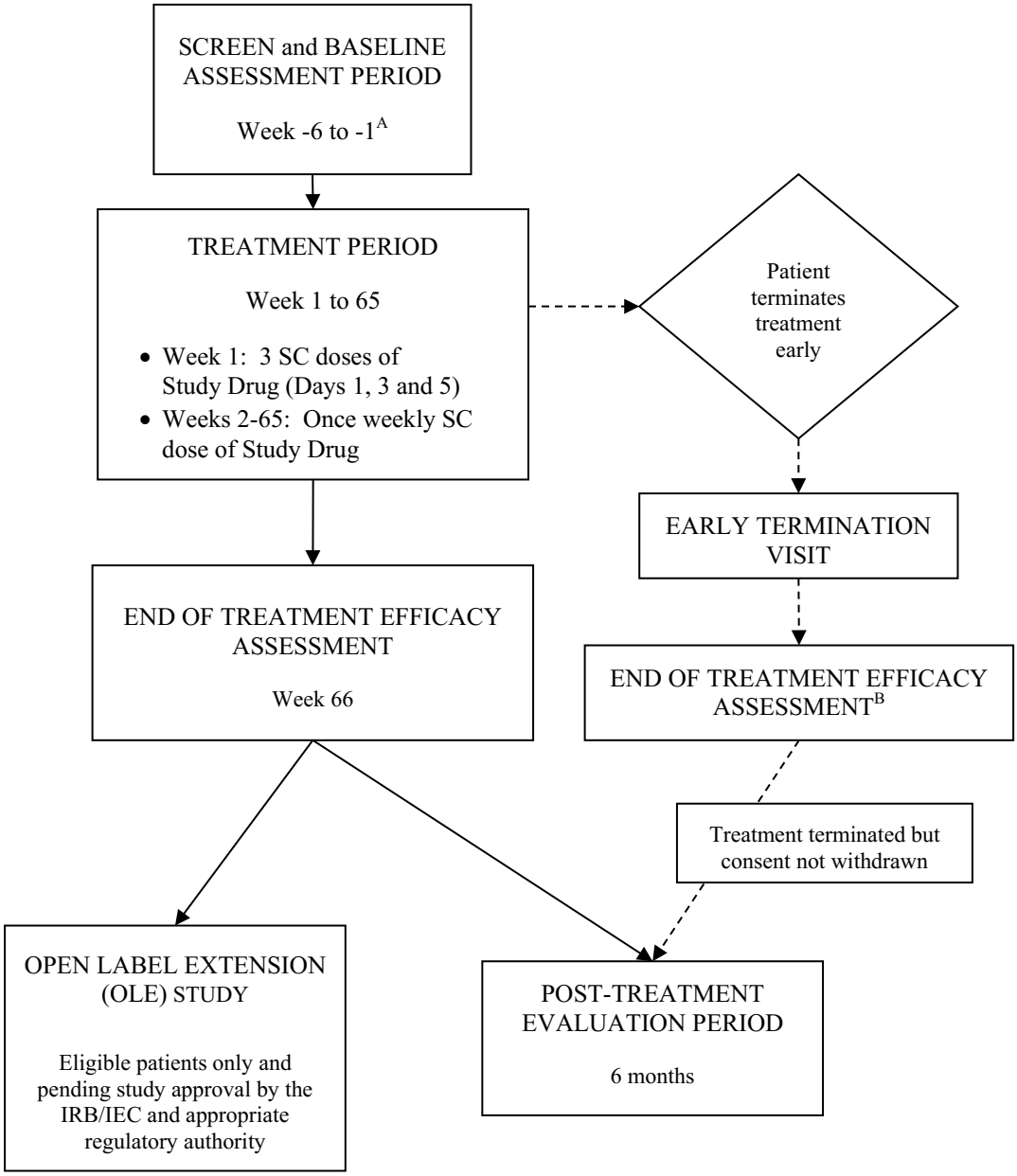
Protocol Synopsis *Continued*

Study Population *Continued*	Exclusion Criteria: *Continued* Additional eligibility criteria for patients participating in the ECHO subgroup: 1. Must have left ventricular wall thickness of ≥ 13 mm on transthoracic echocardiogram at Baseline 2. No known history of persistent hypertension ≥ 150 mm Hg within 12 months prior to Screening 3. Baseline ECHO is evaluable as ascertained by Sponsor central reader
Treatment Groups	Patients will be randomized 2:1 to receive 300 mg ISIS 420915 or placebo
Study Drug Product Dosage and Administration	Study Drug (ISIS 420915 300 mg or placebo) will be administered as subcutaneous (SC) injections in the abdomen, thigh or upper arm
Rationale for Dose and Schedule Selection	300 mg administered 3 times during Week 1 and then once weekly was chosen based on the pharmacokinetic, pharmacodynamic and safety analysis of the ISIS 420915 Phase 1 study in healthy volunteers
Study Visit Schedule and Procedures	The study for an individual patient will generally consist of the following periods: • A ≤ 6-week screening and baseline assessment period • A 65-week treatment period during which Study Drug will be administered as a once weekly SC injection (except during Week 1 where 3 SC injections will be given on alternate days) • A 1-week EOT efficacy assessment period, and • A 6-month post-treatment evaluation period Collection and measurement of vital signs, clinical laboratory parameters (including hematology, serum chemistry, and urinalysis), adverse events, concomitant medication/procedure information, PD parameters (TTR and RBP4), ISIS 420915 plasma trough 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 questionnaire, SF-36 questionnaire, physical examination, PND score, mBMI/BMI, Columbia-Suicide Severity Rating Scale (C-SSRS) questionnaire, ophthalmology examination, electroretinogram (ERG), and electrocardiogram (ECG). All patients will also have a baseline transthoracic ECHO conducted in the screening and baseline assessment period and Week 65 and patients participating in the ECHO subgroup will have a Week 41 ECHO. In addition, approximately 30 patients will have additional pharmacokinetic, ECG, complement, coagulation, hematology, and inflammatory testing at specified visits according to the schedule of procedures (Appendix A). Study Drug will be administered at the Study Center during scheduled clinic visits as outlined in the schedule of procedures (Appendix A). Otherwise, administration of Study Drug may be given by either the Study Center personnel or at home by the patient/caregiver. Dosing instructions and training on injection technique will be provided to the patient where applicable.
Safety and Tolerability Evaluations	The safety and tolerability of ISIS 420915 will be assessed on an ongoing basis by the Study Medical Monitor and by the Independent Data and Safety Monitoring Board (DSMB), as outlined in the Safety Monitoring Plan and DSMB Charter. Safety and tolerability assessments include: adverse events, vital signs, physical examination, clinical laboratory tests, 12 lead ECG, use of concomitant medications, ophthalmology examination, ERG examination, and C-SSRS questionnaire.

Protocol Synopsis *Continued*

Efficacy Evaluations	Efficacy evaluations include change from baseline in mNIS+7, Norfolk QOL-DN questionnaire, mBMI, BMI, and individual components of mNIS+7, NIS+7, and change in GLS by ECHO
Pharmacokinetic Evaluations	Plasma samples will be taken for measurement of ISIS 420915 trough and post-distribution levels at the time points detailed in Appendix A and Appendix C. In a subset of patients, more frequent assessment of pharmacokinetic parameters of ISIS 420915 will be determined as detailed in Appendix A and Appendix C.
Pharmacodynamic Evaluations	Circulating levels of TTR and RBP4 will be determined throughout the study according to schedule of procedures (Appendix A).
Statistical Considerations	The sample size for this study was estimated using published natural history data (Adams et al. 2015) and efficacy data (Berk 2013; Adams 2015) reported in a similar patient population as that targeted in this protocol. The calculations assume an effect size of 9.6 points and standard deviation of 14 in the mNIS+7 score, an effect size of 10.7 and standard deviation of 18 in the Norfolk QOL-DN total score, and a drop-out rate of 25%. One hundred thirty-five (135) patients will give at least 90% and 80% power in the mNIS+7 and Norfolk QOL-DN endpoints, respectively, using a two-sided t-test with an alpha level of 0.05. Eligible patients will be randomized 2:1 (ISIS 420915 : PBO) and stratified for: • Previous treatment with Vyndaqel® (tafamidis) or Diflunisal versus no known previous treatment • Stage 1 versus Stage 2 disease • V30M TTR mutation versus non-V30M TTR mutation The study will enroll approximately 50% Stage 1 and 50% Stage 2 patients. An interim analysis of reduction in TTR level will be performed by an independent statistician and presented to the independent DSMB after approximately 45 patients have completed the Week 13 visit. Details of the analysis and controlled access to the unblinded data are outlined in the Statistical Analysis Plan (SAP) and DSMB Charter. The primary endpoints are the change in the mNIS+7 score and the change in the Norfolk QOL-DN questionnaire total score from baseline to Week 66. The 2 primary endpoints will be analyzed using a ranking strategy with the mNIS+7 tested first and the Norfolk QOL-DN questionnaire total score tested second. Interpretation will be made in a stepwise approach, i.e. should the null hypothesis for the mNIS+7 be rejected, then the null hypothesis for the Norfolk QOL-DN will be tested. However, if the null hypothesis for the mNIS+7 is not rejected, testing for the Norfolk QOL-DN will be considered exploratory. No adjustment will be made for multiple testing (both endpoints will be tested at an alpha of 0.05). Various sensitivity analyses will be conducted to assess the impacts of the stratification factors and the missing values.
Sponsor	Ionis Pharmaceuticals, Inc.

STUDY DESIGN AND TREATMENT SCHEMA



A An exception to the 6-week period given to perform the screening evaluations and baseline assessments is the TTR genotyping and amyloid biopsy tests. These tests may be conducted up to 10 weeks prior to Study Day 1. They are only conducted if appropriate documentation is not already available. In addition, ERG and ophthalmology examinations may be conducted up to 1-week after Study Day 1 if needed for scheduling purposes (except for Ile84 patients that fall under exclusion criteria 3 and should have eye examinations performed to determine eligibility).

B Patients that terminate treatment early should have the early termination visit and EOT efficacy assessments conducted ideally within 14 days from the last dose of Study Drug. They should then enter the post-treatment evaluation period.

Patients that discontinue treatment due to liver transplantation should return to the clinic for the EOT efficacy assessment as soon as feasible after the transplant procedures (if possible within 6 weeks). After the early termination and EOT efficacy assessment procedures are complete, the patient should be withdrawn from the study.

STUDY GLOSSARY

Abbreviation/Acronym	Definition
+7	Sum 7 test. Includes measurements of nerve conduction, vibration threshold and heart rate to deep breathing
Alb/C ratio	Albumin/Creatinine ratio (performed on urine sample)
aPTT	Activated partial thromboplastin time
ASO	Antisense oligonucleotide
AUC	Area under the curve
BMI	Body mass index
CM	Cardiomyopathy
CM-ECHO Set	Patients with a diagnosis of TTR cardiomyopathy at study entry who are not in the ECHO subgroup, plus the patients in the ECHO subgroup
C-SSRS	Columbia-suicide severity rating scale
DSMB	Data and safety monitoring board
ECG	Electrocardiogram
ECHO	Echocardiogram
ECHO Subgroup	The subgroup of patients meeting protocol-specified ECHO criteria and having an additional echocardiogram assessment
EOT	End of treatment
ERG	Electroretinogram
ET	Early termination
FAC	Familial amyloid cardiomyopathy
FAP	Familial amyloid polyneuropathy
GLS	Global longitudinal strain
ICH	International conference on harmonization
IEC	Independent ethics committee
IRB	Institutional review board
IXRS	Interactive voice/web-response system
LLN	Lower limit of normal
mBMI	Modified body mass index (requires determination of plasma albumin levels; mBMI = BMI x serum albumin g/L)
MMRM model	Mixed effect model with repeated measures

mNIS+7	Modified neuropathy impairment score +7. Standard NIS but with modifications made to the +7 component
Modified +7	+7 test with modifications made to the sensory and nerve conduction testing
NIS	Neuropathy impairment score
NIS-LL	Neuropathy impairment score-lower limb
NIS+7	Neuropathy impairment score +7
Norfolk QOL-DN	Norfolk quality of life-diabetic neuropathy questionnaire
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
OLE	Open label extension
OLTX	Orthotopic liver transplantation
P/C ratio	Protein/Creatinine ratio (performed on urine sample)
PD	Pharmacodynamic
PK	Pharmacokinetic
PND Score	Polyneuropathy disability score
RDA	Recommended daily allowance
RBP4	Retinol binding protein 4
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
Study Day 1	Defined as the first day Study Drug is administered to the patient
Study Drug	ISIS 420915 or placebo
SUSARs	Suspected unexpected serious adverse reactions
TTR	Transthyretin
TUCA	Tauroursodeoxycholic acid
ULN	Upper limit of normal
UTR	Untranslated region

1. OBJECTIVES

1.1 Primary Objectives

To evaluate the efficacy of ISIS 420915 as compared to placebo, given for 65 weeks, as measured by the change from baseline in the modified Neuropathy Impairment Score+7 (mNIS+7) and in the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) questionnaire total score, in patients with Familial Amyloid Polyneuropathy (FAP).

1.2 Secondary Objectives

To evaluate the efficacy of ISIS 420915 as compared to placebo based on the change from baseline in the following measures:

- Norfolk QOL-DN questionnaire symptoms domain score in Stage 1 patients and Norfolk QOL-DN questionnaire physical functioning/large fiber neuropathy domain score in Stage 2 patients
- Modified body mass index (mBMI) and body mass index (BMI)
- NIS and modified +7
- NIS+7
- Global longitudinal strain (GLS) by echocardiogram (ECHO) in the ECHO subgroup and in the Cardiomyopathy-ECHO (CM-ECHO) Set

To evaluate the pharmacodynamic (PD) effect of ISIS 420915 as compared to placebo, based on the change from baseline in transthyretin (TTR) and retinol binding protein 4 (RBP4).

To evaluate the safety and tolerability of ISIS 420915.

To evaluate the plasma trough levels of ISIS 420915 in all patients and to evaluate the plasma pharmacokinetic parameters of ISIS 420915 in a subset of patients.

1.3 Tertiary Objectives

To evaluate the change from baseline as compared to placebo in the following measures:

- SF-36 questionnaire
- Individual components of NIS, modified +7, and +7
- + 7
- Individual domain scores of the Norfolk QOL-DN questionnaire

1.4 Exploratory Objectives

To evaluate the change from baseline as compared to placebo, in the following exploratory biomarkers:

- ECHO parameters (except GLS) in the ECHO subgroup and in the CM-ECHO Set

- Plasma N-terminal prohormone of brain natriuretic peptide (NT-proBNP)
- Polyneuropathy disability score (PND)
- Neuropathy symptoms and change (NSC) score

2. BACKGROUND AND RATIONALE

2.1 Overview of Disease

2.1.1 Transthyretin Amyloidosis

Transthyretin is synthesized primarily in the liver and is secreted into the plasma as a 55 KD protein composed of 4 identical subunits of 14 KD each. A major function of TTR in the plasma is to transport retinol (vitamin A) to tissues through an association with retinol binding protein 4 (RBP4). Transthyretin amyloidosis is a rare hereditary disease caused by mutations in the TTR protein. The disease causing mutations destabilize the normal tetrameric structure of TTR causing its dissociation into free monomers and subsequent aggregation into insoluble fibril deposits. These deposits are found in multiple organs including the peripheral nervous system, GI tract and heart. They result in local damage to cells leading to a peripheral polyneuropathy (called Familial Amyloid Polyneuropathy or FAP) and a cardiomyopathy (called Familial Amyloid Cardiomyopathy or FAC).

The main clinical manifestations of FAP are progressive peripheral sensorimotor and autonomic neuropathy. Sensory neuropathy starts in the lower extremities with paresthesias and hypoesthesias of the feet, followed within a few years by motor neuropathy (Sekijima et al. 2009). Gastrointestinal symptoms, characterized by diarrhea and weight loss can also be prominent and reflect autonomic dysfunction (Falk et al. 1997; Ando et al. 2005). Death, on average, occurs within 10 years from symptom onset and is primarily due to malnutrition and cachexia, cardiac disease, sudden death or renal failure (Coelho et al. 2008). FAP can be classified into 3 stages of disease based on ambulatory status: Stage 1 – do not require assistance with ambulation; Stage 2 – require assistance with ambulation; Stage 3 – wheelchair bound (Coutinho et al. 1980). The total worldwide prevalence of FAP has been estimated at approximately 10,000 patients (Coelho et al. 2008).

Clinical trials in patients with FAP have used the Neuropathy Impairment Score (NIS), or derivatives of this score such as the NIS Lower Limb (NIS-LL) or the NIS+7, to assess progression of neuropathy. The NIS score was originally developed for assessment of diabetic neuropathy and is a quantitative score of motor, sensory, and reflex function as judged by the clinician (Dyck et al. 1991). The NIS-LL is a subset of the full NIS and evaluates changes in motor, sensory and reflex activity specifically in the lower limbs whereas the full NIS also evaluates changes in the upper limbs and cranial nerves. The NIS or NIS-LL scores are sometimes combined with the Sum 7 Test (or +7) to give the NIS+7 or NIS-LL+7 composite score (Dyck et al. 1997). The +7 Test is an objective score of large fiber function that includes measurements of nerve conduction, vibration threshold and heart rate to deep breathing (an assessment of autonomic function). Thus the NIS+7 and NIS-LL+7 scores have the advantage of combining a subjective assessment scored by the clinician with objective measurements of autonomic and sensory nerve function, which are both affected in patients with FAP. The

NIS-LL / NIS-LL+7 score is most appropriate to measure neuropathy progression in early Stage 1 FAP patients. But patients in later Stage 1 and Stage 2 (as is the case for this protocol) can reach a ceiling effect on the NIS-LL score, and therefore the full NIS /NIS+7 is a more appropriate score for these patients. However, even the NIS+7 may not be optimally sensitive for assessment of progression of neuropathy in the target population of this study because it is primarily focused on motor function and on large nerve fibers whereas FAP has a significant sensory component and affects both large and small nerve fibers, with a great deal of between patient heterogeneity in the degree to which the different nerve fiber types are affected (Plante-Bordeneuve et al. 2007). Therefore in this study progression of neuropathy will be assessed using a modified NIS+7 score (mNIS+7), which includes a greater sensory component and assesses both large and small nerve fiber function. During the mNIS+7 assessment, the standard NIS+7 assessment will also be collected and the NIS+7 will be analyzed as a secondary endpoint. The NIS score will be used for selection of the target population (inclusion criteria) because there is a greater body of data correlating NIS score with stage of disease. The neuropathy symptom and change (NSC) score is a physician administered questionnaire of the patient's neuropathy symptoms. It is collected during the NIS assessment procedure and will be analyzed as an exploratory endpoint.

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

In FAC patients, TTR amyloid fibrils infiltrate the myocardium, with resultant diastolic dysfunction progressing to restrictive cardiomyopathy and heart failure. The age of onset in FAC patients is between 60 and 70 years and the mean life expectancy from symptom onset is 5-6 years. There is no widely accepted method for measuring progression of cardiac disease in FAC. However, recent studies have shown that strain imaging with echocardiography or MRI can detect changes within a 1-year time frame (Benson et al. 2011; Falk 2011). In addition, the cardiac biomarker N-terminal prohormone of brain natriuretic peptide (NT pro-BNP) has been shown to be elevated in patients with cardiac amyloidosis due to Primary Amyloidosis and to decline as cardiac function improves following removal of the amyloid forming light chain protein with chemotherapy (Palladini et al. 2006). In this study serum NT-proBNP will be assessed as an exploratory endpoint in all patients. One (1) of the more sensitive ECHO parameters, global longitudinal strain, will be assessed as a secondary endpoint. This analysis will be conducted in a subgroup of patients with echocardiographic evidence of cardiac amyloidosis (the ECHO subgroup) and in a subset of patients defined as the CM-ECHO Set. The CM-ECHO Set includes patients with a diagnosis of TTR cardiomyopathy at study entry who are not in the ECHO subgroup, plus the patients in the ECHO subgroup. Other ECHO parameters will be assessed as exploratory endpoints.

2.1.2 Current Therapies

One (1) therapeutic strategy for FAP is orthotopic liver transplantation (OLTX) since most of the amyloidogenic mutated TTR is secreted by the liver. OLTX results in rapid disappearance of mutant TTR protein from the serum, although wild-type TTR protein continues to be produced

by the donor liver and can continue to deposit in the tissues after transplantation (see Section 2.4). The result is that OLT28 May slow the rate of progression of peripheral and/or autonomic neuropathy but usually does not arrest the disease. OLTX is performed on about 120 FAP patients worldwide each year (results from the Familial Amyloid Polyneuropathy World Transplant Registry). Based on prognostic data after liver transplant, current practice is not to perform OLTX on patients with mBMI < 600 or in patients with cardiac involvement. Additionally, it has been observed that poorer prognosis is associated with non-V30M mutations, patients with late onset of disease (> 50 years) or disease duration > 7 years. Therefore, OLTX is generally limited to younger patients early in disease with mild symptoms (typically Stage 1) (Herlenius et al. 2004; Stangou and Hawkins 2004; Okamoto et al. 2009).

In November 2011, the first medication for FAP, Vyndaqel® (tafamidis), was approved under exceptional circumstances in the EU. Vyndaqel® is indicated in the EU for the treatment of transthyretin amyloidosis in adult patients with Stage 1 symptomatic polyneuropathy to delay peripheral neurological impairment (Coelho et al. 2012).

2.2 Therapeutic Rationale

ISIS 420915 is an antisense drug targeted to human TTR mRNA and its hybridization to the cognate TTR mRNA results in the RNase H-mediated degradation of the TTR mRNA, thus preventing production of the TTR protein (see Section 2.3). ISIS 420915 was designed such that it would not hybridize to any other known human gene. The strategy of treating FAP patients with ISIS 420915 is to reduce the levels of mutated and wild-type TTR protein secreted by the liver, a primary organ for antisense oligonucleotide (ASO) distribution after systemic delivery. It should be noted that ASOs are highly charged hydrophilic molecules that do not cross the blood brain barrier (Levin et al. 2008) and thus systemic treatment with ISIS 420915 is not predicted to decrease levels of TTR in the brain. It is predicted that decreasing the amount of liver-derived TTR protein circulating in the plasma by treatment with ISIS 420915 will result in a decrease in the formation of TTR amyloid fibril deposits, and thus slow or halt disease progression. This strategy is a similar strategy to OLTX, with the exception that ISIS 420915 reduces wild-type protein in addition to the mutated protein. Given that wild-type TTR can continue to deposit as amyloid after liver transplant, this distinction may represent a therapeutic advantage.

There is a high unmet medical need for both Stage 1 and Stage 2 FAP patients world-wide. For Stage 2 patients, there is currently no approved therapy and these patients are often not candidates for liver transplant due to advanced age, health reasons, or cardiac involvement. For Stage 1 patients, Vyndaqel® is currently the only approved therapy. However, it is only approved in some countries and is not yet widely reimbursed or established as the standard of care. For these reasons, it is appropriate to utilize a placebo control in this Phase 2/3 study.

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

route of delivery of retinyl esters to peripheral tissues (Wei et al. 1995) and chylomicron-delivered retinyl will not be affected by treatment with ISIS 420915. 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). This is consistent with the findings in the ISIS 420915 chronic monkeys studies where, after 9 months of repeat dosing, no signs of vitamin A deficiency were observed during the ophthalmic examination and histological evaluation of eyes, which included full view examination of the cornea, lens, sclera with attached conjunctiva, anterior and posterior chambers, retina and optic nerve. 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). Although the twins presented with night blindness their symptoms responded to dietary manipulation to ensure adequate dietary vitamin A. Taken together these findings imply that RBP4 is not essential for maintaining adequate tissue retinol levels. To address the potential for impaired retinol delivery to tissues, in this study all patients will be required to take oral supplementation of the recommended daily allowance (RDA) of vitamin A (approximately 3000 IU vitamin A per day). In addition, an ophthalmic examination will be performed at Baseline, after approximately 7 months of treatment, and at the end of treatment. An electroretinogram (ERG) will also be performed at Baseline and at the end of treatment to exclude subclinical tissue retinol deficiency.

2.3 ISIS 420915

2.3.1 Mechanism of Action

ISIS 420915 is a second-generation ASO drug targeted to transthyretin. It is complementary to a region within the 3′ untranslated region (3′UTR) of the transthyretin mRNA and binds to the mRNA by Watson and Crick base pairing. The hybridization (binding) of ISIS 420915 to the cognate mRNA results in the RNase H-mediated degradation of the transthyretin mRNA, thus preventing production of the transthyretin protein. Maximal antisense-mediated reduction of target mRNA levels is typically greater than 90% of control levels in sensitive tissues (Crooke and Bennett 1996; Zhang et al. 2010). Furthermore, reduction in target mRNA levels using this approach correlates directly with a subsequent reduction in target protein levels.

2.3.2 Chemistry

Chemically, ISIS 420915 is a synthetic oligomer of 20 nucleotides (i.e., a 20-mer) that are connected sequentially by phosphorothioate linkages. The nucleotide sequence of ISIS 420915 (Figure 1) is complementary to a 20-nucleotide stretch within the 3′UTR region of the transthyretin protein mRNA. Structurally, the oligonucleotide has 3 regions. Two (2) of them, the 5 nucleotides at the 5′ end and the 5 nucleotides at the 3′ end, are composed of 2′-*O*-(2-methoxyethyl) (MOE)-modified ribonucleotides. These MOE-modified nucleotides confer (1) increased affinity to the target mRNA (Altmann et al. 1996; McKay et al. 1999), (2) increased resistance to exonucleases and endonucleases (thereby increasing stability in tissue)

(Geary et al. 2003), and (3) amelioration of some of the high dose toxicities thereby resulting in an improved safety profile compared to first generation antisense drugs containing phosphorothioate modified oligodeoxynucleotides (DNA) (Henry et al. 2000). The third region, the central portion of the oligonucleotide, is composed of 10 oligodeoxynucleotides. This chimeric design is called a MOE-Gapmer, and ISIS 420915 employs this chimeric structure to enable use of the RNase H-mechanism for antisense activity. This is because while the 2′-MOE modification confers increased stability and affinity, it does not support RNase H catalysis of RNA hybridized to 2′-MOE-modified nucleotides (McKay et al. 1999). This is caused by conformational changes induced in the heteroduplex by 2'-alkoxy:RNA hybrids that are not recognized by RNase H enzymes (Inoue et al. 1987; Monia et al. 1993). By limiting the 2′-MOE modification to nucleotides flanking the phosphorothioate oligodeoxynucleotide core, the beneficial attributes of the 2′-MOE chemistry are preserved while also retaining RNase H recognition.

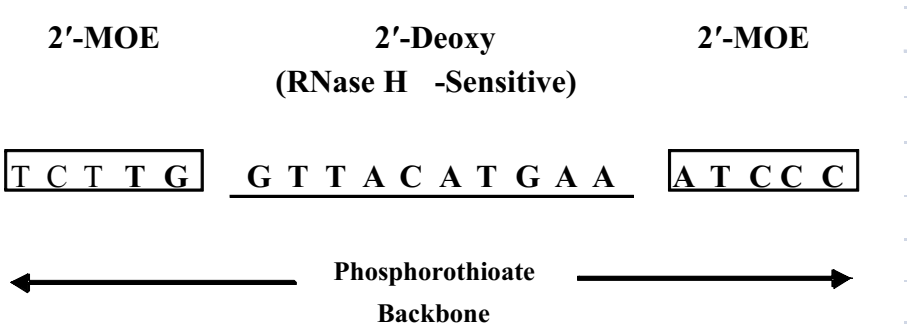


Figure 1 Design of Chimeric 2′-MOE Phosphorothioate Oligonucleotides (MOE-Gapmer). The sequence of ISIS 420915 is shown

2.3.3 Preclinical Experience

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

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

kidneys and liver having the highest concentrations. The half-life in kidney and liver was approximately 13.5 days and 18.8 days, respectively, consistent with the plasma terminal elimination half-life of 17.0 days (at 8 mg/kg) after 4 doses.

2.3.4 Clinical Experience

Detailed information concerning the 1 clinical study (ISIS 420915-CS1) conducted with ISIS 420915 can be found in the Investigator's Brochure. A summary is included below.

ISIS 420915-CS1 was a Phase 1 double-blind, placebo-controlled, dose escalation study designed to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of single and multiple doses of ISIS 420915 administered by subcutaneous injection to healthy subjects. The study enrolled 65 healthy volunteers (16 in the single dose cohorts and 49 in the multiple dose cohorts). Four (4) single dose levels (50, 100, 200, and 400 mg) and 5 multiple dose levels (50, 100, 200, 400 and 300 mg) were evaluated sequentially in the order listed. The allocation of subjects was 3:1 or 8:2 randomized to ISIS 420915 or placebo in the single-dose or multiple-dose cohorts, respectively. Subjects enrolled in the multiple-dose cohorts received a total of 6 doses of Study Drug administered by SC injection: 3 doses on alternate days during the first week (Days 1, 3 and 5) and then once a week for the next 3 weeks (Days 8, 15 and 22).

ISIS 420915 was well-tolerated at the dose levels and dose regimens tested. There were no serious adverse advents (SAE). Two (2) discontinuations were considered possibly related to ISIS 420915, 1 due to constitutional symptoms (400 mg subject) and 1 due to injection site reactions (300 mg subject). The main safety findings included mild injection site reactions characterized most often by pain and erythema. The duration of the reactions were typically 24 hours and resulted from some but not all injections. This injection site reaction profile is considered similar to the profile for other 2′-MOE ASOs. Transient C-reactive protein elevations, primarily associated with the first injection, were observed in nearly all treated subjects at 200 mg multiple-dose or higher. The peak elevations were generally observed 2 days after the first dose of ISIS 420915 (Study Day 3) and resolved within 2 weeks despite continued dosing. For those subjects with C-reactive protein > 10 mg/L, the peak values at Day 3 had a median of 36 mg/L (range from 14 to 169 mg/L). Retinol reductions below the lower limit of normal (LLN) occurred in approximately 50% of subjects treated in the multiple-dose cohorts. The minimum retinol value was 0.19 mg/L (range 0.05 to 0.27 mg/L). Recovery to above the LLN occurred approximately 1-month after the final dose of ISIS 420915. The retinol reduction was an expected consequence of TTR reduction.

2.4 Rationale for Dose and Schedule of Administration

The pharmacokinetics and disposition of many drugs in this class have been characterized and there are remarkable similarities from sequence to sequence and across species. Because distribution to tissues is the dominant mechanism for plasma clearance, it can be assumed that plasma pharmacokinetic similarities translate into similarities in tissue distribution. This assumption is supported by the knowledge that patterns of tissue distribution for oligonucleotides are similar in mice, rats, rabbits, dogs and monkeys (and thus are expected to be similar in humans). Additionally, ASOs are hydrophilic and distribute predominantly to the lean body mass and in our experience they should be administered as a fixed dose, rather than by total body weight.

In FAP (and FAC), both wild-type and mutant TTR protein will deposit in tissue as amyloid. However, it is not known what degree of reduction of TTR will be required to optimally attenuate progression of disease. TTR mutant reductions ≥ 90% have been observed post-liver transplantation (Adams et al. 2000) and have been shown to have a therapeutic effect. Therefore, the therapeutic goal for ISIS 420915 is to reduce both wild-type and mutant plasma TTR levels as much as possible using a dose level that will not cause unacceptable toxicity. Based on data from the TTR knock-out mouse (Episkopou et al. 1993) and from our 9-month chronic toxicology studies in non-human primates, significant target related toxicities are not anticipated even with near complete reduction of TTR. In the ISIS 420915 Phase 1 study, the 300 mg dose level showed a satisfactory safety profile and a substantial pharmacodynamic effect after 6 doses (> 70% mean reduction in plasma TTR levels). The PD effect observed with the 300 mg dose level was also similar to that observed with the 400 mg dose level, and therefore the 300 mg per week dose (with additional loading doses in the first week) was selected for this Phase 2/3 study. Preliminary PK/PD modeling (based on data from the Phase 1 study and extrapolation to steady-state) predicts mean total (wild-type and mutant) TTR steady state reductions of ~80% with either a 300 mg/wk or 400 mg/wk regimen.

A 65-week (15-month) treatment period was selected for this study taking into consideration (1) the time needed to achieve steady-state TTR reductions with ISIS 420915 (~3 months) and (2) data reported for the tafamidis (Vyndaqel®) Phase 3 study, where a clear separation in progression of the NIS-LL score was not observed before 12 months of treatment (EMA Assessment report for Vyndaqel).

The safety data obtained in the ISIS 420915-CS1 study as well as the clinical experience with several other 2′-MOE-modified ASOs (Sewell et al. 2002; Chi et al. 2005; Kastelein et al. 2006) supports the dosing regimen planned for this study. The dosing schedule (loading with 3 doses in Week 1 followed by once weekly SC injections) has been employed safely in previous clinical studies with a number of other phosphorothioate oligonucleotides at doses well in excess of the 300 mg dose utilized in this study. Antisense oligonucleotides of this class have been safely administered intravenously and subcutaneously in multiple clinical studies at doses up to 1000 mg (Kwoh 2008) and treatment duration's ≥ 6 months (Chi et al 2008; Raal et al. 2010) and > 24 months (Santos et al. 2012). The safety and tolerability of the proposed 65-week dosing period is also supported by nonclinical chronic toxicology studies with ISIS 420915.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a Phase 2/3 multicenter, double-blind, randomized, stratified, placebo-controlled study of ISIS 420915 in Stage 1 and Stage 2 FAP patients with a NIS score ≥ 10 and ≤ 130. Approximately 135 patients will be randomized 2:1 (ISIS 420915 : PBO) to receive 300 mg ISIS 420915 or placebo. The study will enroll approximately 50% Stage 1 and 50% Stage 2 patients. Patients will be stratified for:

- Previous treatment with Vyndaqel® (tafamidis) or Diflunisal versus no known previous treatment
- Stage 1 versus Stage 2 disease
- V30M TTR mutation versus non-V30M TTR mutation

Patients will receive 3 SC doses of Study Drug (ISIS 420195 or placebo) during Week 1 on alternate days (Days 1, 3 and 5) followed by once-weekly SC administration during Weeks 2-65 (for a total of 67 doses).

Approximately 20 patients at selected sites will be enrolled in a pharmacokinetic (PK) subgroup and will receive additional sampling for PK, ECG, complement, coagulation, inflammatory, and hematology as specified in the schedule of procedures (Appendix A). In addition, patients that are eligible may consent to participate in the ECHO subgroup and will receive an additional transthoracic ECHO during the treatment period (Appendix A).

The end of treatment (EOT) efficacy assessment is conducted at Week 66 after which patients will enter the post-treatment evaluation period. However, following the EOT efficacy assessment, eligible patients (including patients that received placebo) may elect to enroll in an open-label extension (OLE) study pending study approval by the IRB/IEC and the appropriate regulatory authority. All participating patients in the OLE study will receive once weekly doses of 300 mg ISIS 420915.

3.2 Number of Study Centers

This study will be conducted at multiple centers worldwide.

3.3 Number of Patients

Approximately 135 patients will be randomized in a 2:1 ratio (90 ISIS 420915 : 45 placebo). Any patient who initiated screening and met eligibility criteria at the time of Amendment 7 submission for applicable approvals may be enrolled into the study, even if 135 patients have already been randomized.

3.4 Overall Study Duration and Follow-up

This study will generally consist of the following periods:

- A ≤ 6-week screening and baseline assessment period
- A 65-week treatment period
- A 1-week EOT efficacy assessment period, and
- A 6-month post-treatment evaluation period

3.4.1 Screening and Baseline Assessment

A period of 6 weeks is given to complete the screening and baseline assessments outlined in the schedule of procedures. The baseline assessments should ideally be conducted after patient eligibility has been determined. An exception to the 6-week screening and baseline assessment window is allowed for TTR genotyping and amyloid biopsy which may be conducted up to 10 weeks prior to Study Day 1. In addition, ERG and ophthalmology examinations may be conducted up to 1-week after Study Day 1 if needed for scheduling purposes (except for Ile84 patients that fall under exclusion criteria 3 and should have eye examinations performed to determine eligibility).

3.4.2 Treatment and EOT Efficacy Assessment

The treatment and EOT efficacy assessment period comprises approximately 66 weeks in total. Eligible patients will report to the Study Center for assessments at regular intervals throughout the 65-week treatment period. During the treatment period, Study Drug is administered by SC injections on alternate days during Week 1 (Days 1, 3 and 5), followed by once-weekly SC injections during Weeks 2-65.

After the treatment period is complete, patients will report to the Study Center during Week 66 for the EOT efficacy assessments.

3.4.3 Post-Treatment

The post-treatment evaluation period is 6 months and consists of Study Center visits and additional safety testing. The final study visit is Week 91.

Alternatively, after completion of the EOT efficacy assessment period, eligible patients (including patients that received placebo) may elect to enroll in an OLE study where they will receive weekly doses of 300 mg ISIS 420915, 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 end of study is last patient, last visit.

3.6 Data Safety and Monitoring Board

A Data and Safety Monitoring Board (DSMB) will be assembled to review safety, tolerability and efficacy (as needed) data collected on ISIS 420915 during this study and to review the results of the predetermined TTR interim analysis (see Section 10.4). Based on its ongoing assessment of the safety and tolerability of ISIS 420915, the DSMB will provide recommendations to the Sponsor for modifying, stopping or continuing the study as planned. Details on the safety assessments, frequency of review, meeting schedules and controlled access to unblinded data at the TTR interim analysis are outlined in the DSMB Charter and SAP.

4. PATIENT ENROLLMENT

4.1 Screening

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

Patients must sign the consent form before any screening tests or assessments are performed. At the time of consent the patient will be considered enrolled into the study 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 patient throughout the trial and must be used on all study documentation related to that patient. The screening number and patient identification number must remain constant throughout the entire trial. In the event the patient is

re-consented and re-screened the patient must be given a new screening number. Screening numbers and patient identification numbers, once assigned, will not be re-used.

4.2 Randomization

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

Using an Interactive Voice/Web-Response System (IXRS), eligible patients will be randomized 2:1 to receive ISIS 420915 or placebo, respectively. There will be 2 separate and independent randomizations, 1 for patients in the PK subgroup (approximately 20) and 1 for the other patients who are not in the PK subgroup (approximately 115). Within each randomization, patients will be stratified for:

- Previous treatment with Vyndaqel® or Diflunisal versus no known previous treatment
- Stage 1 versus Stage 2 disease
- V30M TTR mutation versus non-V30M TTR mutation

A permuted block schedule will be used in both randomizations. The Sponsor Quality Assurance department or designee will hold a copy of the randomization lists generated by the IXRS vendor.

4.3 Replacement of Patients

Patients that withdraw from the study will not be replaced.

4.4 Unblinding of Treatment Assignment

The Sponsor, patients, monitors, and Study Center personnel will be blinded throughout the study until all patients have completed the treatment period and the EOT efficacy assessments, and the database has been locked. The DSMB may be unblinded as described in Section 3.6. In order to ensure maintenance of the study blind, TTR, RBP4, and retinol values will not be available to the Sponsor, monitors, Investigators, Study Center Personnel, or the patients. However, if a patient has suffered a Serious Adverse Event (as defined in Section 9.3.3), and/or when knowledge of the treatment assignment will impact the clinical management of the patient, the Investigator will have the ability to unblind the treatment assignment for that patient using the IXRS. The Sponsor or designee will be informed of the unblinding of a patient within 24 hours. In addition, all suspected unexpected serious adverse reactions (SUSARs) will be unblinded by the Sponsor's Drug Safety and Quality Assurance personnel for the purpose of regulatory reporting (see Section 9.2).

Every reasonable attempt should be made to complete the EOT efficacy assessment and early termination study visit procedures and observations (see Appendix A) prior to unblinding, as knowledge of the treatment arm could influence patient assessment.

5. PATIENT ELIGIBILITY

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

5.1 Inclusion Criteria

1. Stage 1 and Stage 2 FAP patients with the following:
   a. NIS score ≥ 10 and ≤ 130
   b. Documented transthyretin variant by genotyping
   c. Documented amyloid deposit by biopsy
2. Willingness to take vitamin A supplements
3. Aged 18 to 82 years old at the time of informed consent
4. Satisfy the following:
   a. Females: Non-pregnant and non-lactating; surgically sterile, post-menopausal, abstinent, or if engaged in sexual relations of child-bearing potential, patient is using an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 3 months after the last dose of Study Drug
   b. Males: Surgically sterile, abstinent, or if engaged in sexual relations of child-bearing potential, patient is utilizing an acceptable contraceptive method (refer to Section 6.3.1) during and for 3 months after the last dose of Study Drug
5. 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

5.2 Exclusion Criteria

1. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator
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. ALT/AST > 1.9 x ULN
   b. Bilirubin ≥ 1.5 x ULN (patients with bilirubin ≥ 1.5 x ULN may be allowed on study following discussion with the Study Medical Monitor if indirect bilirubin only is elevated, ALT/AST is not greater than the ULN and genetic testing confirming Gilbert's disease)
   c. Platelets < 125 x 10^9/L

d. Positive (≥ trace) for protein on urine dipstick. In the event of a positive test eligibility may be confirmed by a quantitative total urine protein measurement of < 1.0 g/24 hours

e. Positive (≥ trace) for blood on urine dipstick. In the event of a positive test eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field. If > 5 red blood cells per high power field and there is a clearly identifiable benign cause for the microscopic hematuria (for example chronic urinary tract infection secondary to neurogenic bladder), eligibility should be determined by discussion with the Study Medical Monitor

f. TSH values outside normal range (unless approved by the Study Medical Monitor)

3. Retinol level at Screen < LLN

   - For patients with a TTR mutation at position 84 (e.g., Ile84Ser or Ile84Asn) and retinol < LLN the exclusion criterion is signs or symptoms of vitamin A deficiency (such as evidence of vitamin A deficiency on ERG)

4. Uncontrolled hypertension (blood pressure > 160/100)

5. Positive test result for human immunodeficiency virus (HIV), hepatitis B or hepatitis C

6. Karnofsky performance status ≤ 50

7. Renal insufficiency as defined by estimated creatinine clearance calculated according to the formula of CKD-EPI < 60 mL/min/1.73 m^2 at Screen. If the calculated creatinine clearance is thought to be artificially low, a 24-hour urine creatinine clearance can be completed with prior Sponsor approval

8. Presence of known type 1 or type 2 diabetes mellitus

9. Other causes of sensorimotor or autonomic neuropathy (e.g., autoimmune disease)

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. If previously treated with Vyndaqel® must have discontinued treatment for 2 weeks prior to Study Day 1. If previously treated with Diflunisal, must have discontinued treatment for 3 days prior to Study Day 1

12. Previous treatment with any oligonucleotide or siRNA within 6 months of screening. Subjects that have been previously treated with oligonucleotides should be approved by the Study Medical Monitor

13. Prior liver transplant or anticipated liver transplant within 1 year of screening

14. New York Heart Association (NYHA) functional classification of ≥ 3

15. Acute coronary syndrome or major surgery within 3 months of screening

16. Known Primary Amyloidosis
17. Known Leptomeningeal Amyloidosis
18. Anticipated survival less than 2 years
19. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1
20. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated. Patients with a history of other malignancies that have been curatively treated may be eligible but must be discussed and approved by the Sponsor Medical Monitor
21. 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
22. Known Monoclonal Gammopathy of Undetermined Significance or Multiple Myeloma

5.3 Additional Eligibility Criteria for Patients Participating in the ECHO Subgroup

1. Must have left ventricular wall thickness of ≥ 13 mm on transthoracic echocardiogram at Baseline
2. No known history of persistent hypertension ≥ 150 mm Hg within 12 months prior to screening
3. Baseline ECHO is evaluable as ascertained by the Sponsor central reader

6. STUDY PROCEDURES

6.1 Study Schedule

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

6.1.1 Screening and Baseline Assessment Period

Before any study-specific procedures or evaluations are initiated, patients must sign and date the informed consent form. A 6-week period is given to perform the screening evaluations and baselines assessments which must be completed before Study Day 1. Exceptions are the ERG, and ophthalmology examinations that may be conducted up to 1-week after Study Day 1 if needed for scheduling purposes (except for Ile84 patients that fall under exclusion criteria 3 and should have eye examinations performed to determine eligibility). In addition, the TTR genotyping and amyloid biopsy tests may be conducted up to 10 weeks prior to Study Day 1. These tests are only conducted if appropriate documentation is not already available. The baseline assessments should ideally be performed after patient eligibility has been determined. An abnormal screening result may be retested for review by the Study Medical Monitor for eligibility purposes.

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

The baseline assessments include mNIS+7 (which is performed twice), Norfolk QOL-DN questionnaire, transthoracic ECHO, 24 hour urine collection, ERG exam, ophthalmology exam, vital signs, and a blood draw for chemistry.

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

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

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

6.1.2 Treatment Period

During Study Week 1, patients will report to the Study Center for evaluations and Study Drug administration on Days 1, 3 and 5. After Week 1, Study Drug will be administered once weekly. Patients will report to the Study Center for Study Drug administration, evaluations, and tests regularly throughout the treatment period and will have weekly safety testing according to the Schedule of Procedures in Appendix A. During a clinic visit, all blood samples should be drawn prior to Study Drug administration (exceptions are the post-dose samples in the PK subgroup). For weeks that do not include a clinic visit, Study Drug may be administered by either Study Center personnel (in which case additional clinic visits will occur) or at home by the patient/caregiver (see Section 8.1). Every effort should be made to ensure the previous week's dose is given 7 days prior to a scheduled clinic visit. Dosing instructions and training will be provided to the patient where applicable.

To help reduce patient travel burden, some clinic visits and weekly safety testing between visits may be done as non-clinic visits. For non-clinic visits, collection of vital signs and labs (as indicated in the Schedule of Procedures) can be performed by the Sponsor's home healthcare service or by a local laboratory with prior Sponsor approval.

In addition to Study Drug, patients will also receive daily supplemental doses of the recommended daily allowance (RDA) of vitamin A (approximately 3000 IU vitamin A or closest approximate dose as available in the region in which the patient resides). Vitamin A may be provided as either a single vitamin A supplement, or as part of a multivitamin. The vitamin A supplement should be taken throughout the treatment and post-treatment evaluation period.

A mNIS+7 assessment and Norfolk QOL-DN questionnaire are conducted at Week 35 (D239) and must be conducted approximately > 24 hours from the previous week's dose. The Norfolk QOL-DN questionnaire should be administered prior to the mNIS+7 assessment. The Week 35 D239 and D240 assessments may be done on the same day.

For Weeks 3-15 there is a ± 2 day and for Weeks 18-65 there is a ± 5 day visit 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.

During the treatment period, an ophthalmology examination will be performed at Week 29 and Week 65, and an electroretinogram (ERG) examination will be performed at Week 65. The Week 65 ophthalmology and ERG examinations may be done at Week 59 if needed for scheduling purposes. A window of ± 2 weeks is allowed for the Week 29 and Week 65 (or Week 59) eye examinations.

Patients with a TTR mutation at position 84 and with retinol levels < LLN at Screening, will be required to have 2 additional ophthalmology examinations at approximately 3 and 11 months after the first dose.

Echocardiogram (ECHO) Subgroup Only

In addition to ECHOs conducted at Baseline, early termination, and Week 65 for all patients, patients who qualify and consent to participate in the ECHO subgroup will have an additional ECHO conducted during the treatment period at Week 41, which can be done at Week 47 if the patient elects to have a Home Healthcare visit at Week 41. All ECHO assessments have a window of ± 2 weeks.

Pharmacokinetic (PK) Subgroup Only

A subgroup of approximately 20 patients to ensure approximately 15 patients with evaluable PK data after early withdrawals (at selected sites only), will participate in the PK subgroup. Patients in this subgroup will have more frequent pharmacokinetic sampling in order to evaluate the plasma pharmacokinetic parameters of ISIS 420915. Patients will also have additional post-dose sampling for ECG, inflammatory, coagulation, hematology, and complement. Patients in this subgroup will have additional visits to the clinic to collect a 24-hour post-dose blood draw after dosing on Day 1, and a 24 hour, 3 day and 7 post-dose blood draw after dosing on Day 240 (Week 35) and Day 449 (Week 65). Alternatively, the additional visits needed to collect the 24 hour, 3 day and 7 day post-dose blood draw may be collected by the Sponsor appointed home healthcare service.

A patient participating in either the PK or ECHO subgroups may withdraw consent for the subgroup specific procedures (e.g., echocardiogram, multiple blood draws for PK) without being withdrawn from dosing or from the study. If a patient withdraws consent from the subgroup procedures, he/she should remain on study and continue to follow all the non-subgroup assessments and procedures as outlined in Appendix A.

6.1.3 EOT Efficacy Assessment Period

The EOT efficacy assessment is conducted at Week 66 and consists of a minimum of 2 visits to allow for 2 measurements of the mNIS+7. Both assessments must be performed on separate days and within 14 days from the last dose of Study Drug. The first mNIS+7 assessment must be conducted approximately > 24 hours from the last dose of Study Drug. In addition, every effort should be made to conduct the 2 assessments < 7 days apart. The Norfolk QOL-DN questionnaire should be given on the same day as the first mNIS+7 assessment, but **prior** to the mNIS+7 assessment.

The Week 66 EOT efficacy assessment should also be performed on patients that terminate from treatment early. In this case, the early termination visit and EOT efficacy assessment should be performed within 14 days after the last dose of Study Drug. In the event that this does not occur, the early termination visit and EOT assessments should be performed as soon as possible. The 2 mNIS+7 assessments must be conducted on separate days. In addition, every effort should be made to conduct the 2 assessments < 7 days apart.

6.1.4 Post-Treatment Period

After completion of the EOT efficacy assessment, patients will enter the 6-month post-treatment evaluation period and will report to the study center and have weekly platelet monitoring for a minimum of 6 weeks after the last dose of Study Drug which may be collected by the clinic, Sponsor's home healthcare service or by a local laboratory as outlined in the schedule of procedures (Appendix A). At Week 71, adverse events should be collected by the site personal through a phone contact with the patient if a clinic visit was not conducted.

Alternatively, after completion of the EOT efficacy assessment, eligible patients may elect to receive ISIS 420915 in an OLE study (ISIS 420915-CS3), 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 but weekly platelet monitoring should continue between the last dose of Study Drug in CS2 and the first dose of Study Drug in CS3. If this period extends beyond 6 weeks, the frequency will be determined by the Study Medical Monitor.

6.2 Additional Study Assessments

6.2.1 Laboratory Assessments

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

6.2.2 Congestive Heart Failure

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

- Chest x-ray
- 12 lead ECG
- Echocardiogram

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

6.2.3 Arrhythmias

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

- 12 lead ECG
- Echocardiogram

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

6.2.4 Myocardial Ischemia

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

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

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

6.2.5 Event-Specific Supplemental CRF Pages

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

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

6.3 Restriction on the Lifestyle of Patients

6.3.1 Contraception Requirements

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

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

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

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

For male patients:

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

For female patients:

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

***Note: A female condom and a male condom should not be used together as friction between the 2 can result in either product failing**

6.3.2 Other Requirements

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

7. STUDY DRUG

7.1 ISIS 420915 or Placebo

Study Drug (ISIS 420915 or placebo) characteristics are listed in Table 1.

The Study Drug is contained in stoppered glass vials and will be provided to the Study Center by the Sponsor. The Study Drug storage and preparation instructions will be provided by the Sponsor. For long term storage at clinical sites, the Study Drug must be stored securely at 2° to 8° Celsius and be protected from light.

Table 1 Study Drug Characteristics

Study Drug	ISIS 420915	Placebo
Strength	200 mg/mL	NA
Volume/Formulation	1 mL solution per 2 mL vial or 1.5 mL solution per 3 mL vial	1 mL solution per 2 mL vial or 1.5 mL solution per 3 mL vial
Route of Administration	SC 1.5 mL	SC 1.5 mL

7.2 Packaging and Labeling

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

7.3 Study Drug Accountability

The study staff is required to document the receipt, dispensing, and return of Study Drug supplies provided by the Sponsor. The Study Center must return all used and unused Study Drug to the Sponsor or designee.

8. TREATMENT OF PATIENTS

8.1 Study Drug Administration

For each individual patient, Study Drug will be administered subcutaneously as a single 1.5 mL injection 3 times in the first week and then once weekly for Weeks 2-65. For weeks with a clinic visit, Study Drug will be administered at the clinic. For weeks that do not include a clinic visit, Study Drug may be administered by either Study Center personnel or at home by the patient/caregiver. Every effort should be made to ensure the previous week's dose is given 7 days prior to a scheduled clinic visit. If Study Drug is to be administered at home, dosing instructions and training will be provided to the patient by the Study Center personnel.

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

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

8.2 Other Protocol-Required Drugs

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

8.3 Other Protocol-Required Treatment Procedures

There are no other protocol required treatment procedures.

8.4 Treatment Precautions

There are no specific treatment precautions required for this study.

8.5 Safety Monitoring Rules

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

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

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

Stopping Rule Guidance: In the event of an initial clinical laboratory result that meets a stopping criterion, patients must not be re-dosed until a confirmatory test result has been reviewed by the Study Medical Monitor. If any of the stopping criteria described below (refer to Sections 8.6.1 to 8.6.3) are met and are confirmed, the patient will be permanently discontinued from further treatment with Study Drug (ISIS 420915 or placebo), evaluated fully as outlined below and in consultation with the Study Medical Monitor or appropriately qualified designee, and will be entered into the post-treatment evaluation portion of the study (after completing the early termination and EOT efficacy assessments). In general, patients who do not meet the stopping rules based upon retest may continue dosing. However, the Investigator and the Study Medical Monitor (or appropriately qualified designee) should confer as to whether additional close monitoring of the patient is appropriate.

Additional Guidance: If possible, a pharmacokinetic sample should be collected as soon as possible after an SAE has occurred (preferably within 2 weeks). In addition, if a patient is asked to return to the clinic for additional evaluations due to an AE, then a pharmacokinetic sample should be taken at the time of the unscheduled visit.

8.5.1 Safety Monitoring Rules for Liver Chemistry Tests

The following rules are adapted from the draft guidance for industry, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," issued by the U.S. Department of Health and Human Services, Food and Drug Administration, July 2009.

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

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

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

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

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

8.5.2 Safety Monitoring Rules for Renal Function

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

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

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

c. Urine Alb/C ratio > 5 x ULN

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

* urine collection should be performed at the same time as the protocol specified collection of serum creatinine (see Appendix A)

** baseline is Wk1D1 value

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

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

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

8.5.3 Safety Monitoring Rules for Ocular Effects

All patients should receive an ophthalmology examination by an eye specialist at Baseline, after approximately 7 months of receiving Study Drug (Week 29) and also at the end of the dosing period (Week 65). An ERG will also be performed at Baseline and the end of the dosing period (Week 65). In addition, any patient that complains of persistent ocular symptoms compatible with vitamin A deficiency (e.g., night blindness or dry eyes) should be referred for an ophthalmology examination. If the ophthalmologist confirms the patient's symptoms are consistent with vitamin A deficiency and/or the examination reveals physical findings that are consistent with vitamin A deficiency (but do not reach the stopping rule criteria described in Section 8.6.4) then an ERG examination should be conducted and analyzed by the central reader. In addition, it is suggested that a review of diet and supplement use and an evaluation for factors which may contribute to low vitamin A levels such as infection, alcohol consumption, and zinc and/or iron deficiency be conducted.

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

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

a) Changes from baseline > 50%, and

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

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

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

8.5.4 Safety Monitoring Rules for Platelet Count Results

Platelets will be monitored weekly throughout the treatment period and for a minimum of 6 weeks after the last dose of Study Drug (this includes early termination patients as well as patients that complete the full 65-week treatment period). For patients participating in the Post-Treatment Evaluation Period, frequency of testing after the Week 71 visit will be determined by the Investigator in consultation with the Study Medical Monitor. For patients participating in the ISIS 420915-CS3 study, weekly monitoring should continue between the last dose of Study Drug in CS2 and first dose of Study Drug in CS3. If this period extends beyond 6 weeks, the frequency of monitoring will be determined by the Study Medical Monitor.

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

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

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

8.6 Stopping Rules

8.6.1 Stopping Rules for Liver Chemistry Elevations

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

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

8.6.2 Stopping Rules for Renal Function Test Results

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

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

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

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

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

8.6.3 Stopping Rule for Platelet Count Results

In the event of a confirmed platelet count less than 75,000/mm^3, and in the presence of major bleeding or clinically-relevant non-major bleeding (defined below; Schulman et al. 2005), dosing of a patient with Study Drug (ISIS 420915 or placebo) will be stopped permanently. The follow-up schedule for any events meeting this stopping criterion will be determined by the Investigator in consultation with the Study Medical Monitor.

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

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

Definition major bleeding events:

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

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

Definition clinically-relevant, non-major bleeding events:

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

8.6.4 Stopping Rule for Ocular Effects

A patient should be permanently discontinued from Study Drug if an ERG is changed from baseline and shows clear signs of vitamin A deficiency (as described in Section 8.5.3) and an ophthalmology examination reveals significant changes from baseline in any 1 of certain physical signs (Bitot's spots, xerophthalmic ulcers, keratomalacia, or other signs and symptoms of corneal necrosis) and a consultation with the central reader has occurred.

8.6.5 Stopping Rule for QTc Prolongation

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

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

The suitability of the patient for continued dosing, the need for any modification to treatment schedule or dose (refer to Section 8.7) and the most appropriate follow-up schedule, will be determined by the Investigator in consultation with the Study Medical Monitor. Suitability of continued dosing will be based on factors such as clinical symptoms, width of QRS complex, presence or absence of paced rhythm, and the firing of a defibrillator (in the case that the patient

has an implantable defibrillator). In addition, consideration should be given to an expert cardiology read of the patients' ECGs and a cardiology consult. If a patient is deemed suitable for continued dosing, more frequent ECGs will be performed, with the frequency to be determined by the Investigator and Study Medical Monitor. Any additional monitoring/investigation will also be determined by the Investigator and Study Medical Monitor.

8.7 Adjustment of Dose and/or Treatment Schedule

Adjustments of dose and/or treatment schedule should occur only on rare occasions. Up to 2 adjustments in the treatment schedule may be allowed for patients that are unable to tolerate the once weekly dose (for example if platelet counts fall below 75,000/mm^3 as described in Section 8.6.3). Any proposed adjustment to treatment schedule or dose level must be discussed with, and approved by, the Study Medical Monitor prior to initiation. If the patient remains stable after adjustment, they may be cautiously returned to the original dose/regimen after consultation with the Study Medical Monitor.

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

8.8 Discontinuation of Study Treatment

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

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

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

Patients that discontinue from treatment are encouraged to remain in the study. Every effort should be made to complete the early termination visit and the EOT efficacy assessment followed by all post-treatment evaluation visits. If the patient declines to participate in the post-treatment evaluation visits, at a minimum, the early termination visit and EOT efficacy assessment procedures should be performed at the time of withdrawal (See Appendix A) and ideally within 14 days from the last dose of Study Drug. If early termination assessments are to be performed on a day with mNIS+7 EOT assessment, the mNIS+7 assessment should be performed first.

8.9 Withdrawal of Patients from the Study

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

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

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

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

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

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

For patients who receive a liver transplant, every effort should be made to complete the EOT efficacy assessment as soon as feasible after the transplant procedures (if possible within 6 weeks). After the EOT efficacy assessment and early termination visit is complete, patients should be withdrawn from the study.

8.10 Concomitant Therapy and Procedures

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

8.10.1 Concomitant Therapy

A concomitant therapy is any non-protocol specified drug or substance (including over-the-counter medications, herbal medications and vitamin supplements) administered between signing of informed consent and Week 91 visit.

Allowed Concomitant Therapy

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

Disallowed Concomitant Therapy

Patients are required to take daily RDA supplemental doses of vitamin A during the treatment and post-treatment evaluation periods. The vitamin A supplements will be provided by the Study Center or designee. A patient may choose to substitute the Study Center provided vitamin A supplement with 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).

Doxycycline, and tauroursodeoxycholic acid (TUCA) are not allowed unless approved by the Study Medical Monitor. If a patient is taking doxycycline or TUCA they should discontinue treatment at least 4 days prior to Study Day 1.

Treatment with either Vyndaqel® or Diflunisal is not allowed at any time during the treatment period and ideally should not be taken during the post-treatment follow-up period. If Vyndaqel® or Diflunisal are taken in the post-treatment period, the Study Medical Monitor should be consulted to determine if an additional mNIS+7 assessment should be collected prior to initiating Vyndaqel® or Diflunisal treatment.

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

8.10.2 Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between signing of informed consent and Week 91 visit.

8.11 Treatment Compliance

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

The Study Center staff is required to document the receipt, dispensing, and return of Study Drug supplies. Patients that are self-administering Study Drug at home must record treatment in a provided dosing diary that will be reviewed by the Study Center staff and Clinical Monitor.

9. SERIOUS AND NON-SERIOUS ADVERSE EVENT REPORTING

9.1 Sponsor Review of Safety Information

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

9.2 Regulatory Requirements

The Sponsor is responsible for regulatory submissions and reporting to the Investigators of serious adverse events (SAEs) including SUSARs per the International Conference on

Harmonization (ICH) guidelines E2A and ICH E6. Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines.

IRB/IEC will be notified of any SAE according to applicable regulations. The Data and Safety Monitoring Board (DSMB) will be notified of any SAE as specified in the DSMB charter.

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

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

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

9.3 Definitions

9.3.1 Adverse Event

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

9.3.2 Adverse Reaction and Suspected Adverse Reaction

An adverse reaction is any adverse event caused by the Study Drug.

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

9.3.3 Serious Adverse Event (SAE)

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

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

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

  Hospitalization is defined as an admission of greater than 24 hours to a medical facility and does not always qualify as an AE.

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

9.4 Monitoring and Recording Adverse Events

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

9.4.1 Serious Adverse Events

In the interest of patient safety, and in order to fulfill regulatory requirements**,** all SAEs (regardless of their relationship to Study Drug) should be reported to the Sponsor or designee within 24 hours of the Study Center's first knowledge of the event. The collection of SAEs will begin after the patient signs the informed consent form and stop at the end of the patient's follow-up period which is defined as the Week 91 visit or the EOT efficacy assessment for patients that will enroll into the OLE. When the Investigator is reporting by telephone, it is important to speak to someone in person versus leaving a message. An Initial Serious Adverse Event Form should be completed and a copy should be faxed to the Sponsor or designee.

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

9.4.2 Non-Serious Adverse Events

The recording of non-serious AEs will begin after the patient signs the informed consent form and will stop at the end of the patient's follow-up period, which is defined as the Week 91 visit, or the EOT efficacy assessment for patient's that will enroll into the OLE. The Investigator will monitor each patient closely and record all observed or volunteered AEs on the Adverse Event Case Report Form.

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

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

9.4.3.1 Relationship to the Study Drug

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

- **Related:** There is clear evidence that the event is related to the use of Study Drug e.g., confirmation by positive re-challenge test
- **Possible:** The event cannot be explained by the patient's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and Study Drug administration
- **Unlikely/Remote:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to Study Drug 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 Study Drug

9.4.3.2 Severity

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

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

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

9.4.3.3 Action Taken with Study Drug

Action taken with Study Drug due to the event is characterized by the following.

- **None:** No changes were made to Study Drug administration and dose
- **Permanently Discontinued:** Study Drug 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 CRF as appropriate).

9.4.3.5 Outcome of the Adverse Event

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

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

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

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

9.5 Procedures for Handling Special Situations

9.5.1 Abnormalities of Laboratory Tests

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

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

9.5.2 Prescheduled or Elective Procedures or Routinely Scheduled Treatments

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

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

9.5.3 Dosing Errors

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

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

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

9.5.4 Contraception and Pregnancy

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

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

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

Female patients: If a suspected pregnancy occurs while on the study (including follow-up), a pregnancy test will be performed. The patient with a confirmed pregnancy will be immediately

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

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

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Subsets, and Covariates

10.1.1 Primary Endpoints

The primary endpoints are the change in mNIS+7 score from baseline to Week 66 and the change in the Norfolk QOL-DN questionnaire total score from baseline to Week 66.

10.1.2 Secondary Endpoints

10.1.2.1 Secondary Efficacy Endpoints

- Change in the Norfolk QOL-DN questionnaire symptoms domain score (Stage 1 patients only) and Norfolk QOL-DN questionnaire physical functioning/large fiber neuropathy domain score (Stage 2 patients only) from baseline to Week 66
- Change in the mBMI and BMI from baseline to Week 65
- Change in NIS and modified +7 from baseline to Week 66
- Change in NIS +7 score from baseline to Week 66
- Change in GLS by ECHO from baseline to Week 65 in the ECHO subgroup and in the CM-ECHO Set

10.1.2.2 Pharmacodynamic Endpoint

- Change from baseline in TTR level to Week 65
- Change from baseline in RBP4 level to Week 65

10.1.2.3 Safety Endpoints

- Adverse events
- Vital signs and weight
- Physical examination
- Clinical laboratory tests
- ECG
- Use of concomitant medication
- Ophthalmology and ERG examinations
- Columbia-Suicide Severity Rating Scale
- Thyroid panel
- Inflammatory panel
- Coagulation
- Complement
- Immunogenicity

10.1.2.4 Pharmacokinetic Endpoints

Selected ISIS 420915 post-distribution plasma concentrations (i.e., trough and various post-treatment time points) will be measured throughout the study and the estimated plasma terminal elimination half-life ($t_{1/2\lambda z}$) after end of treatment will be calculated (when possible). In evaluable patients from the PK subgroup, additional selected plasma PK parameters (as outlined in Section 10.5.4) will also be determined after dosing on Days 1, 240, and 449. Further details of the various planned plasma PK assessments are outlined in Section 10.5.4.

10.1.3 Tertiary Endpoint

- Change from baseline to Week 65 in SF-36 questionnaire domain scores
- Change from baseline to Week 66 in the individual components of the NIS (cranial, muscle weakness, reflexes and sensory), modified +7 (heart rate to deep breathing, nerve conduction, heat-pain sensory and touch-pressure sensory testing), and +7 (vibration detection threshold and nerve conduction)
- Change from baseline to Week 66 in +7
- Change from baseline to Week 66 in individual domain scores of Norfolk QOL-DN (physical functioning/large fiber neuropathy, symptoms, activities of daily living, small fiber neuropathy and autonomic neuropathy)

10.1.4 Exploratory Endpoints

- Change from baseline in echocardiogram parameters (except GLS) in the ECHO subgroup and in the CM-ECHO Set
- Change from baseline in NT-proBNP
- Change from baseline in the PND score
- Change from baseline in the NSC score
- Change from baseline in retinol
- Change from baseline in retinyl palmitate

10.2 Sample Size Considerations

The sample size for this study was estimated using information published from the placebo controlled Phase 3 Diflunisal trial (Berk et al. 2013), a retrospective, multinational natural history study in 283 FAP patients (Adams et al. 2015), and uncontrolled data using another TTR mRNA targeted therapeutic (Adams 2015). It is estimated that the placebo group will have a 16 point increase in the mNIS+7 score from baseline to Month 15, and the treated group will have a 6.4 point increase in mNIS+7. The standard deviation of the change from baseline in each treatment group is estimated to be 14. With 135 patients (2:1 allocation ratio) there would be at least 90% power to detect a 9.6 point difference in the change from baseline in the mNIS+7 score between the 2 groups, with a 2-sided t-test of 5% alpha, assuming that the dropout rate is approximately 25%.

For the Norfolk QOL-DN questionnaire total score, it is estimated that the placebo group will have a 13.3 point change from baseline to Month 15, the treated group will have a 2.6 point change from baseline and the standard deviation of the change from baseline in each treatment group will be 18. With 135 patients, there would be at least 80% power to detect a 10.7 point difference in the change from baseline in the Norfolk QOL total score between the 2 groups, with a 2-sided 5% alpha, assuming that the dropout rate is approximately 25%.

10.3 Populations

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

The Safety Set will include all randomized patients who received at least 1 injection of Study Drug.

The Per-Protocol Set will include the subset of the Full Analysis Set that have received at least a certain percentage of the prescribed doses of Study Drug and that have no significant protocol deviations that would be expected to affect efficacy assessments. The detailed criteria will be specified and finalized prior to conducting the primary analysis (i.e., exact criteria to determine inclusion in or exclusion from the Per Protocol Set will be determined for each patient prior to conducting the primary analysis).

The Pharmacokinetic Set will include the subset of the Safety Set that has at least 1 evaluable PK result.

The ECHO subgroup will include the subset of the Safety Set that has at least 1 evaluable post baseline ECHO assessment and participated in the ECHO substudy. The CM-ECHO Set will include the subset of the Safety Set that has at least 1 evaluable post baseline ECHO assessment and had a diagnosis of TTR cardiomyopathy at study entry but are not in the ECHO subgroup, plus patients who participated in the ECHO subgroup.

10.4 Interim Analysis

A pharmacodynamic interim analysis of reduction in plasma TTR level will be performed by the independent statistician and reviewed by the DSMB after approximately 45 patients have completed the Week 13 visit. This interim will be a futility analysis, so there will be no statistical penalty assigned. The results of this interim analysis will result in a decision to continue the study as planned or to stop the study. Details of the analysis and controlled access to the unblinded data are outlined in the SAP and DSMB Charter.

10.5 Planned Methods of Analysis

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

Descriptive summary statistics including n, mean, median, standard deviation, interquartile range (25th percentile, 75th percentile), and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data by treatment group. 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 tertiary efficacy and pharmacodynamic endpoints, except GLS 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. ECHO endpoints including GLS will be assessed in the ECHO subgroup and in the CM-ECHO Set.

10.5.1 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.

10.5.2 Safety Analysis

Treatment duration and amount of Study Drug received will be summarized by treatment group, as well as reasons for withdrawal from Study Drug.

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

Laboratory tests to ensure patient safety including chemistry panel, complete blood count with differential, coagulation panel, and complement, will be summarized by study visits for each treatment group. These safety variables will also be presented as change and percent change from baseline over time after Study Drug administration, as appropriate.

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

10.5.3 Efficacy Analysis

The 2 primary endpoints (mNIS+7 and Norfolk QOL-DN questionnaire total score) will be analyzed using a ranking strategy with the mNIS+7 tested first and the Norfolk QOL-DN tested second. The primary efficacy analyses will be (1) the comparison of change from baseline to Week 66 in mNIS+7 between ISIS 420915 300 mg group and placebo group in the Full Analysis Set and (2) the comparison of change from baseline to Week 66 in Norfolk QOL-DN questionnaire total score between ISIS 420915 300 mg group and placebo group in the Full Analysis set. Interpretation will be made in a stepwise approach, i.e. should the null hypothesis for the mNIS+7 be rejected, then the null hypothesis for the Norfolk QOL-DN questionnaire total score will be tested. However, if the null hypothesis for the mNIS+7 is not rejected, testing for the Norfolk QOL-DN questionnaire total score will be considered exploratory. No adjustment will be made for multiple testing (both endpoints will be tested at an alpha of 0.05).

The data will be analyzed using a Mixed Effects Model with Repeated Measures (MMRM model) where the treatment group, time, 3 randomization stratification factors, and treatment by time interaction will be included in the model as fixed effects; patient will be a random effect. The baseline by time interaction will be included if appropriate. No imputation for missing data will be made. The 2 assessments at each timepoint (except Week 35 that includes only 1 assessment) will be averaged at component level.

For each primary endpoint, a cumulative distribution function plot will be used to show the distribution of change from baseline to Week 66 in individual patients by treatment group.

The primary efficacy analyses will take place after all patients have completed the treatment and EOT efficacy assessments and the database has been locked. Evaluation of the model will be performed. The details of model checking and alternative analyses approach will be provided in the SAP that will be finalized prior to the final database lock.

The following sensitivity analyses will be conducted for both of the primary efficacy endpoints, and details of the analysis are outlined in the SAP:

- Comparison of change from baseline to Week 66 in mNIS+7 score and Norfolk QOL-DN questionnaire total score between ISIS 420915 300 mg and placebo group in the Per-Protocol Set
- A variety of multiple imputation methods will be used to investigate the impact of different patterns of missing data

- Addition of pooled investigative site to the primary efficacy MMRM model, where pooled site will be specified in the SAP prior to unblinding. The interaction between treatment and pooled site will be examined if model convergence permits

- Responder analysis (for mNIS+7 only) to examine if the improvement in response is consistent over a range of response thresholds. If a patient terminates treatment early due to AE or lack of efficacy or other types of treatment failure, then the response of the patient is considered as non-responder. Other missing values are considered as censoring

    - For the set of response thresholds, the proportion of responders will be plotted against the responder threshold by treatment group

Secondary efficacy analyses include:

- Comparison of change from baseline to Week 66 in the Norfolk QOL-DN questionnaire symptoms domain score (Stage 1 patients) and Norfolk QOL-DN questionnaire physical functioning/large fiber neuropathy domain score (Stage 2 patients) between ISIS 420915 300 mg and placebo group in the Full Analysis Set

- Comparison of change from baseline to Week 65 in mBMI and BMI between ISIS 420915 300 mg and placebo group in the Full Analysis Set

- Comparison of change from baseline to Week 66 in the NIS, modified +7, and NIS+7 between ISIS 420915 300 mg and placebo group in the Full Analysis Set. Comparison of change from baseline to Week 66 in Norfolk QOL-DN domain scores (symptoms domain for Stage 1 patients and physical functioning/large fiber neuropathy domain for Stage 2 patients), NIS, modified +7 and NIS+7, and change from baseline to Week 65 in mBMI and BMI between ISIS 420915 300 mg and placebo group in the Per-Protocol Set

- Comparison of change from baseline to Week 65 in GLS by ECHO in the ECHO subgroup and in the CM-ECHO Set

Tertiary analyses include:

Comparisons of change from baseline to Week 65 in SF-36 questionnaire domain scores, and change from baseline to Week 66 in individual components of NIS (cranial, muscle weakness, reflexes and sensory), modified +7 (heart rate to deep breathing, nerve conduction, heat-pain sensory and touch-pressure sensory testing) and +7 (vibration detection threshold and nerve conduction), +7, and individual domain scores of Norfolk QOL-DN (physical functioning/large fiber neuropathy, symptoms, activities of daily living, small fiber neuropathy and autonomic neuropathy) between ISIS 420915 300 mg and placebo group in both Full Analysis Set and Per-Protocol set. The secondary and tertiary analyses except GLS will be conducted in the same way as for the primary endpoint. The analysis for GLS by ECHO in the ECHO subgroup and in the CM-ECHO Set will be specified in the ECHO SAP.

10.5.4 Pharmacokinetic Analysis

For all patients, pre-dose ISIS 420915 plasma concentrations will be summarized using descriptive statistics. In addition, non-compartmental pharmacokinetic analysis of ISIS 420915 concentrations will be carried out on each individual patient data set, and the plasma disposition half-life ($t_{1/2\lambda z}$) associated with the apparent terminal elimination phase will be calculated, if appropriate, using available data (Day 449 and later), from the equation, $t_{1/2\lambda z} = 0.693/\lambda_z$, where λ_z is the rate constant associated with the apparent terminal elimination phase.

For patients in the PK subgroup only, non-compartmental pharmacokinetic analysis of ISIS 420915 will be carried out on each individual patient data set. 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. Following single dosing (Day 1), area under the plasma concentration-time curve from zero time (pre-dose) to 24 hours after the dose ($AUC_{0\text{-}24hr}$) will be calculated using the linear trapezoidal rule. Following multiple dosing (Days 240 and 449), $AUC_{0\text{-}24hr}$ and area under the plasma concentration-time curve during the time of each sampled dosing interval (tau,τ) at steady-state (AUC_τ) will be calculated using the linear trapezoidal rule. Other pharmacokinetic parameters, as appropriate, may be determined or calculated at the discretion of the pharmacokinetic scientist.

Plasma pharmacokinetic parameters will be summarized using descriptive statistics. Additional details regarding the pharmacokinetic analysis will be described in the SAP.

There is no statistical rationale for the selected sample size of the PK subgroup. The PK subgroup size of approximately 20 patients (to give approximately 10 evaluable patients in the treated group assuming a dropout rate of 25%) was selected based upon prior clinical PK experience with ISIS 420915 and other 2′-MOE-modified ASOs, and expected low-to- moderate inter- and intra-patient variability in PK parameter measures.

10.5.5 Pharmacodynamic Analysis

Pharmacodynamic analyses include comparisons of change from baseline in TTR and RBP4 between ISIS 420915 300 mg and placebo group. The data will be analyzed in the same way as for the primary endpoint and will be assessed in both the Full Analysis and Per-protocol populations.

10.5.6 Exploratory Analysis

Exploratory analysis includes the comparisons of change from baseline in ECHO parameters except GLS (ECHO subgroup and CM-ECHO Set), NT-ProBNP, PND score and NSC score to Week 65 (Week 66 for NSC) between ISIS 420915 300 mg and placebo group. Details of the analysis will be provided in the SAP and ECHO SAP.

11. INVESTIGATOR'S REGULATORY OBLIGATIONS

11.1 Informed Consent

The written informed consent document should be prepared in the language(s) of the potential patient population, from 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 Study Drug products are administered. The patient must be given sufficient time to consider whether to participate in the study.

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

11.2 Ethical Conduct of the Study

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

11.3 Independent Ethics Committee/Institutional Review Board

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

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

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

11.4 Patient Confidentiality

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

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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments

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

12.2 Study Termination

The Sponsor reserves the right to terminate the study, according to the terms of the study contract. The Sponsor should notify the IEC/IRB in writing of the trial's completion or early termination.

12.3 Study Documentation and Storage

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

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

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

- Patient files containing completed case report forms, patient dosing diaries, informed consents, and supporting copies of source documentation
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation and all correspondence to and from the IEC/IRB and the Sponsor

- If drug supplies are maintained at the Study Center, proof of receipt, Study Drug Product Accountability Record, Return of Study Drug Product for Destruction, Final Study Drug Product Reconciliation Statement, 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 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 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 for concomitant medications should be recorded in English if possible, unless it is a combination drug, then record the trade name in English.

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

12.6 Compensation for Injury

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

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14. APPENDICES

Appendix A Schedule of Procedures

Appendix A Schedule of Procedures

	Screen	Baseline Assess-ments	Treatment (65 Wks)																												EOT Efficacy
Study Week	W -6 to -1[1]		W 1			W 3	W 5	W 8	W 10	W 13	W 15	W 18	W 20	W 23	W 26	W 29	W 32	W 35		W 38	W 41	W 44	W 47	W 50	W 53	W 56	W 59	W 62	W 65	W 66
Study Day	S-42 to S-1		D 1	D 3	D 5	D 15	D 29	D 50	D 64	D 85	D 99	D 120	D 134	D 155	D 176	D 197	D 218	D 239	D 240	D 260	D 281	D 302	D 323	D 344	D 365	D 386	D 407	D 428	D 449	D 456
Visit Window (+/- Days)			0	0	0	2	2	2	2	2	2	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	7
Informed Consent	X																													
Inclusion/Exclusion	X																													
Medical History	X																													
Height	X																													
HIV, Hepatitis B & C	X																													
Biopsy for Amyloid[3]	X																													
TTR Genotyping[3]	X																													
Study Drug Admin.			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	
Physical Exam	X		X					X		X									X										X	
Vital Signs[A] (BP[4], HR, RR, temp)	X	X	X	X	X	X	X	X		X		X		X		X		X	X		X		X		X		X		X	X
ECG (12-Lead, triplicate)	X		X[C]					X[A]											X[A]										X[A]	
Pregnancy Test[5]	X		X[A]							X						X					X				X				X	
Chemistry Panel (Fasting)[A]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X			X		X		X		X		X		X	
Serum Creatinine (Fasting)																	X			X		X		X		X		X		
Hematology[A]	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
Weekly Platelet Monitoring[10]			← Weekly Platelet Monitoring →																											
Urinalysis[A]	X	X	X			X	X	X	X	X	X	X	X	X	X	X			X		X		X		X		X		X	
24 hour Urine		X																												
Thyroid Panel[A]	X		X							X						X							X						X	
Inflammatory Panel[A]			X	X	X	X	X	X		X									X										X	
PT, aPTT, INR[A]			X		X	X	X	X											X										X	
Complement (C3)[A]			X																											
Immunogenicity[A]			X				X			X						X							X						X	
AE & Conmeds & Concomitant Procedures	X	X	X	X	X	X	X	X		X		X		X		X		X	X		X		X		X		X		X	X

Appendix A Schedule of Procedures *Continued*

	Screen	Baseline Assess-ments	Treatment (65 Wks)																												EOT Efficacy
Study Week	W		W			W	W	W	W	W	W	W	W	W	W	W	W	W		W	W	W	W	W	W	W	W	W	W	W	W
	-6 to -1[1]		1			3	5	8	10	13	15	18	20	23	26	29	32	35		38	41	44	47	50	53	56	59	62	65	66
Study Day	S-42 to S-1		D 1	D 3	D 5	D 15	D 29	D 50	D 64	D 85	D 99	D 120	D 134	D 155	D 176	D 197	D 218	D 239	D 240	D 260	D 281	D 302	D 323	D 344	D 365	D 386	D 407	D 428	D 449	D 456
Visit Window (+/- Days)			0	0	0	2	2	2	2	2	2	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	7
NIS[6]	X																													
mNIS+7 Assessment[7]		2X																X												2X
Norfolk QOL-DN[7]		X																X												X
SF-36 Questionnaire[A]			X																X										X	
PND Score			X																X										X	
Body Weight (Fasting)	X		X							X									X					X					X	
PD Panel (Fasting)[A]	X		X			X	X	X		X		X		X		X			X		X		X		X		X			X	
PK Trough[A]			X			X	X	X		X		X		X		X			X		X		X		X		X			X	
Transthoracic ECHO[8]		X																			X									X	
NT-proBNP[A]			X							X									X											X	
Retinol (Fasting)[A]	X		X				X			X						X							X							X	
ERG Exam[9]		X																												X	
Ophthalmology Exam[9]		X														X														X	
C-SSRS			X[A]							X						X							X							X	
Additional Tests for PK Subgroup Only (n = 20)																															
PK AUC/Trough Blood			X[B]	X[A]	X[A]	X[A]	X[A]	X[A]		X[A]		X[A]		X[A]		X[A]			X[F]		X[A]		X[A]		X[A]		X[A]		X[F]	
ECG (12-Lead, triplicate)	X		X[C]																X[C]										X[C]	
Complement (C5a, Bb)			X[C]		X[A]	X[A]	X[A]	X[A]											X[C]										X[C]	
PT, INR, aPTT			X[D]		X[A]	X[A]	X[A]	X[A]											X[D]										X[D]	
Inflammatory Panel			X[A]	X[A]	X[A]	X[A]	X[A]	X[A]		X[A]									X[E]										X[E]	
Hematology	X		X[A]	X[A]	X[A]	X[A]	X[A]	X[A]	X[A]	X[A]	X[A]	X[A]	X[A]	X[A]	X[A]	X[A]	X[A]		X[E]	X[A]	X[A]	X[A]	X[A]	X[A]	X[A]	X[A]	X[A]	X[A]	X[A]	X[E]	

Appendix A Schedule of Procedures *Continued*

Post Treatment Evaluation Period

	Post-Treatment Evaluation Period (6 Mo)[2]								Early Term
Study Week	W 67	W 69	W 71	W 74	W 77	W 80	W 83	W 91	
Study Day	D 463	D 477	D 491	D 512	D 533	D 554	D 575	D 631	
Visit Window (+/- Days)	7	7	7	7	7	7	7	7	
Informed Consent									
Inclusion/Exclusion									
Medical History									
Height									
HIV, Hepatitis B & C									
Biopsy for Amyloid[3]									
TTR Genotyping[3]									
Study Drug Admin.									
Physical Exam								X	X
Vital Signs[A] (BP[4], HR, RR, temp)			X		X			X	X
ECG (12-Lead, triplicate)								X	X
Pregnancy Test[5]					X			X	X
Chemistry Panel (Fasting) [A]			X		X			X	X
Serum Creatinine (Fasting)	X	X		X		X	X		
Hematology [A]	X	X	X	X	X	X	X	X	X
Weekly Platelet Monitoring[10]	Weekly Platelet Monitoring								
Urinalysis [A]								X	X
24 hour Urine									
Thyroid Panel[A]								X	X
Inflammatory Panel[A]			X					X	X
PT, aPTT, INR[A]								X	X
Complement (C3)[A]									
Immunogenicity[A]			X					X	X
AE & Conmeds & Concomitant Procedures			X		X			X	X

Appendix A Schedule of Procedures *Continued*

Post Treatment Evaluation Period

	Post-Treatment Evaluation Period (6 Mo)[2]								Early Term
Study Week	W 67	W 69	W 71	W 74	W 77	W 80	W 83	W 91	
Study Day	D 463	D 477	D 491	D 512	D 533	D 554	D 575	D 631	
Visit Window (+/- Days)	7	7	7	7	7	7	7	7	
NIS[6]									
mNIS+7 Assessment[7]								X	EOT
Norfolk QOL-DN[7]								X	EOT
SF-36 Questionnaire[A]								X	X
PND Score								X	X
Body Weight (Fasting)					X			X	X
PD Panel (Fasting)[A]			X		X			X	X
PK Trough[A]			X		X			X	X
Transthoracic ECHO[8]									X
NT-proBNP[A]					X			X	X
Retinol (Fasting)[A]			X		X			X	X
ERG Exam[9]									X
Ophthalmology Exam[9]									X
C-SSRS								X	X
Additional Tests for PK Subgroup Only (n = 20)									
PK AUC/Trough Blood			X		X			X	X
ECG (12-Lead, triplicate)								X	X
Complement (C5a, Bb)								X	X
PT, INR, aPTT								X	X
Inflammatory Panel			X					X	X
Hematology	X[A]	X[A]	X	X[A]	X	X[A]	X[A]	X	X

Note: If not specifically labeled, “X” means anytime. Shaded columns represent visits with the option to be completed in clinic, by a home healthcare service, or by a local laboratory with prior Sponsor approval.

Appendix A Schedule of Procedures *Continued*

1 A 6-week period is given to complete the screening/baseline assessments. Ideally, the baseline assessments should be conducted after patient eligibility is determined.

2 After completing the Week 66 efficacy assessments, patients will enter the post-treatment evaluation period. However, eligible patients may elect to enroll 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.

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

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

5 For females of child-bearing potential only, by serum βhCG except on Day 1 were urine hCG is tested pre-dose.

6 At Screening for determination of eligibility only (+7 not needed). For an individual patient, every effort should be made to use the same NIS evaluator throughout the study and the NIS evaluator must be insulated from the patient's general study procedures and knowledge of the patient's adverse events.

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

- Two (2) independent mNIS+7 assessments will be performed at Baseline on separate days. Both assessments should be performed within 14 days prior to the first dose of Study Drug (Day 1). In addition, every effort should be made to conduct the two assessments < 7 days apart.
- mNIS+7 and Norfolk QOL-DN assessments at Week 35 (D239) must be conducted approximately > 24 hours from the previous weeks dose.
- Two independent mNIS+7 assessments will be performed at Week 66 on separate days. Both assessments must be performed within 14 days from the last dose of Study Drug. The first mNIS+7 assessment must be conducted approximately > 24 hours from the last dose of Study Drug. In addition, every effort should be made to conduct the two assessments < 7 days apart. The EOT efficacy assessment should also be performed on patients that terminate treatment early, ideally within 14 days of the last dose of Study Drug.

8 Transthoracic ECHO

- The baseline, Week 65 and early term ECHOs are conducted on all patients.
- The Week 41 ECHO is only conducted in patients participating in the ECHO subgroup and can be done at Week 47 if the patient elects to have a Home Healthcare visit at Week 41.
- There is a window of ± 2 weeks for all ECHOs.

9 ERG and ophthalmology examinations

- The Week 29 and Week 65 examinations have a window of ± 2 weeks. The baseline ERG and ophthalmology examinations may be done up to 1-week after Study Day 1 if needed for scheduling purposes (except for Ile84 patients that fall under exclusion criteria 3 and should have eye examinations performed to determine eligibility). Week 65 ERG and ophthalmology examinations may be done at Week 59 if needed for scheduling purposes.
- The early termination (Early term) ERG and ophthalmology examinations are only done if the patient discontinues treatment after ≥ 9 mo of dosing.

Appendix A Schedule of Procedures *Continued*

Legend Continued

10 Weekly platelet monitoring is required throughout the treatment period and for a minimum of 6 weeks after the last dose of Study Drug (this includes early termination patients as well as patients that complete the full 65 week treatment period). For patients participating in the Post-Treatment Evaluation Period, frequency of testing after the Week 71 visit will be determined by the Study Medical Monitor in consultation with the Investigator. For patients participating in the ISIS 420915-CS3 study, weekly monitoring should continue between the last dose of Study Drug in CS2 and first dose of Study Drug in CS3. If this period extends beyond 6 weeks, the frequency will be determined by the Study Medical Monitor.

The following visits to collect platelet values are required in addition to the visits shown in the table. These visits do not have specified windows to allow flexibility of scheduling but with the intent that platelets are assessed each calendar week. Visits may be completed in clinic, by home healthcare service, or by a local laboratory:

Week 2, 4, 6, 7, 9, 11, 12, 14, 16, 17, 19, 21, 22, 24, 25, 27, 28, 30, 31, 33, 34, 36, 37, 39, 40, 42, 43, 45, 46, 48, 49, 51, 52, 54, 55, 57, 58, 60, 61, 63, 64, 66, 68, and 70

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

A Pre-dose (during treatment period)
B Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24-hour
C Pre-dose, 3-hour
D Pre-dose, 3 and 12-hour
E Pre-dose, 24-hour, 3-day and 7-day
F Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24-hour, 3-day and 7-day. For both E and F: where applicable, the 7-day blood draw should be taken before the next weekly dose is given. The 12-hr blood draw is encouraged but optional.

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 ISIS 420915 or other similar oligonucleotides

Clinical Chemistry Panel
- Sodium
- Potassium
- Chloride
- Bicarbonate
- Total protein
- Albumin
- Calcium
- Magnesium
- Phosphorus
- Glucose
- BUN
- Creatinine
- Uric Acid
- Total bilirubin
- Direct (conjugated) bilirubin
- Indirect (unconjugated) bilirubin
- ALT
- AST
- Alkaline phosphatase
- Creatine kinase
- Estimated creatinine clearance (CKD-EPI)
- Total IgM
- Total IgG

Screening Tests
- Hepatitis B surface antigen
- Hepatitis C antibody
- HIV antibody
- Serum βhCG
- Urine hCG
- FSH

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

Complement[1]
- C3
- C5a
- Bb

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

24 hour Urine[1]
- Creatinine
- Protein
- Albumin

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

Pharmacokinetics[2]
- ISIS 420915 levels in plasma

Thyroid Panel
- Thyroid stimulating hormone (TSH)
- Free T4 (FT4)

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

Inflammatory Panel[1]
- hsCRP

Others
- Retinol
- Retinyl Palmitate
- NT-proBNP
- Immunogenicity

1 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.

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 to assess other actions of ISIS 420915 with plasma constituents

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

Appendix C PK Sampling Schedule

Appendix C PK Sampling Schedule

PK Sampling Schedule (All Patients except PK Subgroup)

D1 (Wk 1)	D15 (Wk3)	D29 (Wk 5)	D50 (Wk 8)	D85 (Wk 13)	D120 (Wk 18)	D155 (Wk 23)	D197 (Wk 29)	D240 (Wk 35)	D281 (Wk 41)	D323 (Wk 47)	D365 (Wk 53)	D407 (Wk 59)	D449 (Wk 65)	D491 (Wk 71)	D533 (Wk 77)	D631 (Wk 91)
Blood: Predose	Blood: Predose	Blood: Predose	Blood: Predose	Blood: Predose	Blood: Predose	Blood: Predose	Blood: Predose	Blood: Predose	Blood: Predose	Blood: Predose	Blood: Predose	Blood: Predose	Blood: Predose	Blood: Anytime	Blood: Anytime	Blood: Anytime

Extensive PK Sampling Schedule – (PK Subgroup Only)[1]

D1 (Wk 1)	D3 (Wk 1)	D5 (Wk 1)	D15 (Wk 3)	D29 (Wk 5)	D50 (Wk 8)	D85 (Wk 13)	D120 (Wk 18)	D155 (Wk 23)	D197 (Wk 29)	D240 (Wk 35)	D281 (Wk 41)	D323 (Wk 47)	D365 (Wk 53)	D407 (Wk 59)	D449 (Wk 65)	D491 (Wk 71)	D533 (Wk 77)	D631 (Wk 91)
Blood: Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 hours Post SC Injection	Blood: Pre-dose	Blood: Pre-dose	Blood: Pre-Dose	Blood: Pre-dose	Blood: Pre-dose	Blood: Pre-dose	Blood: Pre-dose	Blood: Pre-dose	Blood: Pre-dose	Blood: Predose 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 hours, 3 days, 7 days Post SC Injection	Blood: Pre-dose	Blood: Pre-dose	Blood: Pre-dose	Blood: Pre-dose	Blood: Predose 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 hours, 3 days, 7 days Post SC Injection	Blood: Any-time	Blood: Any-time	Blood: Any-time

1 The 12-hr time-point is encouraged but optional