Statistical Analysis Plan

A Phase 2, Open-label Extension Study to Evaluate the Long-Term Safety, Clinical Activity and Pharmacokinetics of Revusiran (ALN-TTRSC) in Patients with Transthyretin (TTR) Cardiac Amyloidosis Who Have Previously Received revusiran.

Protocol Number:	TTRSC-003
Protocol Version and Date:	Original: 20 May 2014 Amendment 1: 10 July 2014 Amendment 2: 23 October 2014
Name of Test Drug:	revusiran (ALN-TTRSC)
Phase:	Phase 2
Methodology:	Open-label in Patients with TTR Cardiac Amyloidosis
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Tel: +1 (617) 551-8200 Fax: +1 (617) 551-8101
Sponsor Representative:	[redacted] Senior Vice President, Clinical Development
Analysis Plan Date:	August 4, 2015
Analysis Plan Version:	Final Version 1.0

AUTHOR SIGNATURE PAGE

Protocol Title: A Phase 2, Open-label Extension Study to Evaluate the Long-Term Safety, Clinical Activity and Pharmacokinetics of revusiran in Patients with Transthyretin (TTR) Cardiac Amyloidosis Who Have Previously Received revusiran

Sponsor: Alnylam Pharmaceuticals, Inc.
300 Third Street,
Cambridge, MA 02142 USA

Protocol Number: TTRSC-003

Document Date / Version: August 4, 2015 / Final Version 1.0

Author: [redacted]
Senior Manager, Biometrics
Alnylam Pharmaceuticals, Inc.
300 Third Street,
Cambridge, MA 02142 USA

Signature: [redacted]

Date: 4 AUG 2015

APPROVAL SIGNATURE PAGE

Signatories:

[redacted]
Senior Director, Clinical Research

Signature: [redacted]

Date: 4 AUG 2015

[redacted]
Senior Director, Head of Biometrics

Signature: [redacted]

Date: 4AUG 2015

[redacted]
Senior Vice President, Clinical Development

Signature: [redacted]

Date: 5 AUG 2015.

TABLE OF CONTENTS

ABBREVIATIONS

Abbreviation	Definition
6-MWD	6-minute Walk Distance
^{99m}Tc	^{99m}-Technetium
AE	Adverse event
ATC	Anatomic Therapeutic Class
AUC	Area under the curve
CI	Confidence interval
CMR	Cardiac magnetic resonance imaging (cardiac MRI)
CTCAE	Common Terminology for Clinical Adverse Events
CV	Cardiovascular
DILI	Drug Induced Liver Injury
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EQ-5D	EQ-5D Quality of Life questionnaire
ET	Early termination
FAC	Familial amyloidotic cardiomyopathy
HF	Heart failure
KCCQ	Kansas City Cardiomyopathy Questionnaire
LFT	Liver function test
mBMI	Modified body mass index
NT-proBNP	N-terminal prohormone of B-type natriuretic peptide
NYHA	New York Heart Association
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
QOL	Quality of life
SAE	Serious adverse event
SEM	Standard error of the mean
SSA	Senile systemic amyloidosis
TEAE	Treatment-emergent adverse event
TTR	Transthyretin
ULN	Upper limit of normal

1. INTRODUCTION

Study ALN-TTRSC-003 is an open-label, extension study designed to evaluate the long-term safety, clinical activity, and pharmacokinetic (PK) activity of subcutaneously administered revusiran in patients with transthyretin (TTR) cardiac amyloidosis. Approximately 25 patients who completed study ALN-TTRSC-002 will be enrolled in this extension study.

Eligible patients will receive 5 daily doses of 500 mg revusiran and a dose at Day 7. Thereafter, weekly doses will be administered for the duration of the study. Visits to the clinical study center take place during dose initiation and approximately every 12 weeks through the end of study (Day 672), and for a safety follow-up visit.

The safety and tolerability of long-term administration of revusiran will be assessed throughout the study. Evaluation of pharmacodynamic (PD) and pharmacokinetic parameters will occur at various time points. Clinical efficacy, disease burden, and healthcare utilization will also be explored and exploratory biomarkers will be evaluated.

The purpose of this Statistical Analysis Plan is to summarize key analyses to be conducted for each objective and presented in the clinical study report. Pharmacokinetic analysis is out of scope and will be described in another document. Tables, Listings, and Figures will be described separately.

2. OBJECTIVES OF THE STUDY

2.1. Primary Objective:

- To evaluate the safety and tolerability of long-term dosing with revusiran

2.2. Secondary Objectives:

- To assess the PD effect of long-term dosing of revusiran on serum levels of TTR
- To assess clinical effects of long-term dosing of revusiran, including effect on mortality, hospitalizations and 6-MWD

2.3. Tertiary Objectives:

- To further characterize the PK of revusiran
- To assess the clinical effects of revusiran including: echocardiogram, cardiac biomarkers (N-terminal prohormone of B-type natriuretic peptide [NT-proBNP] and troponin T and I), quantification of amyloid in fat pad aspirates, cardiac magnetic resonance imaging [CMR], Kansas City Cardiomyopathy Questionnaire [KCCQ], ^{99m}Technetium [^{99m}Tc] imaging, estimated glomerular filtration rate [eGFR], New York Heart Association [NYHA] class, modified body mass index [mBMI], new onset or recurrence of atrial fibrillation, pacemaker placement, change in diuretic regimen, and EQ-5D Quality of Life [QOL] questionnaire
- To understand disease burden and health care utilization

3. DEFINITIONS

Variables	Definition
Baseline (for Safety Analyses)	Last value prior to first dose of revusiran in this extension study.
Baseline (for PD parameters)	For each PD parameter, the baseline will be the average of all values prior to the first dose of revusiran in this extension study.
Baseline (for 6MWD)	Last value prior to the first dose of revusiran in this extension study [If the patient only has screening visits, then the longer distance recorded of the 2 screening values as the baseline value will be selected]. If the patient does not have any pre-dose values in this extension study, then the latest value recorded distance from the parent study (TTRSC-002) will be selected.
Baseline (for other clinical endpoints)	Latest results prior to the first dose of revusiran in this extension study. If there is no result prior to the first dose of revusiran in this extension study, then the latest measurement from the parent study (TTRSC-002) will be used as the baseline value.
Relative Fold	Follow-up Value ÷ Baseline Value
Percentage Change	((Follow-up Value – Baseline Value)/Baseline Value) x 100

4. POPULATIONS

Population	Definition
Safety Analysis Set	All patients who receive at least one dose of revusiran in this study
PD Analysis Set	All patients who receive at least 1 dose of revusiran in this study and have at least 1 blood sample post-dose assessment
PK Analysis Set	All patients who receive at least one dose of revusiran and have at least one blood draw post-dose to determine plasma concentrations of revusiran

Safety Analysis Set will be used to analyze all safety and efficacy analyses. PD Analysis Set will be used to analyze PD analyses. PK Analysis set will be used to analyze PK analyses.

5. PROTOCOL VIOLATIONS/DEVIATIONS

Patients who experience one or more major protocol violations as determined by review will be identified prior to database lock. All major violations and protocol deviations will be presented in a patient listing.

6. MISSING DATA

For continuous and categorical variables (with the exception of calculating AUC for PD parameters), data will be analyzed as reported, unless otherwise specified.

Imputation for AUC calculation of PD parameters: Patients who discontinued prematurely from the study will have their last PD value carried forward to impute all subsequent visits.

7. STATISTICAL METHODOLOGY

7.1. General Methods:

All study data will be presented in patient data listings. Statistical analyses will be descriptive.

Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be presented for continuous variables.

Frequencies and percentages will be presented for categorical and ordinal variables. If there are missing values, the number of missing values will be presented, but without a percentage. Percentages will be based on the number of non-missing values.

Means and medians will be reported to one decimal place more than the precision of the recorded data. Standard deviations will be reported to two decimal places more than the recorded data. Minimum and maximum values will be reported to the same precision as recorded in eCRF or external data.

Any repeated measurement prior to first date of dose will be treated as a valid individual measurement and used in the derivation of baseline. Post-dose visits will be mapped to scheduled visits based on the corresponding visit windows provided in the schedule of events for each visit (see Appendix 5).

7.2. Primary Objective:

- To evaluate the safety and tolerability of long-term dosing with revusiran

Parameters: Safety and tolerability assessments for revusiran will include study drug exposure, adverse events (AEs), clinical laboratory parameters (hematology, serum chemistry, thyroid function, coagulation, and urinalysis), vital signs (oral body temperature, blood pressure, heart rate, and respiration rate), 12-lead electrocardiograms (ECGs), prior and concomitant medication monitoring, physical examinations, and eye examinations.

Analysis: These analyses will use the Safety Analysis Data Set. Data will be tabulated for all treated patients.

Exposure: Study drug exposure will include summaries of frequencies (percentage) of patients who completed dose during time periods. We will also summarize the number of patients with a dose interruption and the number of interruptions per patient over time course of the study. Additionally, a summary of the number of patients who self-administered dose at home will be reported overall and by time periods.

Adverse Events: Treatment-emergent adverse events (TEAEs) will be defined as any AE occurring or worsening in severity after the first dose (including date/time) of study drug administration. TEAEs will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA) by System Organ Class (SOC) and Preferred Term (PT). An overview of the frequency (percentage) of TEAEs will be tabulated (such as but not limited to, the number of patients with at least 1 TEAE, the number of patients with at least 1 TEAE related to study drug, the number of patients with at least 1 SAE). Separate tabulations will be produced for all TEAEs, TEAEs by maximum severity, treatment-related TEAEs, treatment-related TEAEs by severity, serious adverse events (SAEs), discontinuation from study drug due to AEs and deaths. Patient listings will generated for all patients who discontinued due to death and discontinued from study drug.

Clinical Laboratory Parameters: Clinical laboratory parameters (hematology, serum chemistry, thyroid function, coagulation, and urinalysis), which are continuous variables, will have a tabular summary of descriptive statistics (mean, standard deviation, median, quartiles, minimum, and maximum; Appendix 3). These tabular summaries will display descriptive statistics of actual value, change from baseline and percentage change from baseline at each visit. Plots of group means (± standard error of the mean [SEM]) and per-patient plots for each parameter will be generated.

For clinical laboratory parameters of interest, an outlier analysis will be conducted to summarize the total frequency (percentage) of values (across all visits) above certain thresholds (eg, ≤ upper limit of normal [ULN], >ULN, >2×ULN, etc.). Thresholds will depend on the clinical laboratory parameter. For all labs, a shift table will be generated to examine the proportion of results >ULN and results<lower limit of normal [LLN].

Vital Signs: The analysis of vital signs will focus on the percentage of clinically relevant abnormalities. The number of patients evaluated and the number (percentage) of patients with clinically relevant post-baseline abnormalities will be presented. Descriptive statistics at each visit for vital sign (oral body temperature, blood pressure, heart rate, and respiration rate) will also be summarized. All findings of physical examinations will be presented in a data listing.

ECG: ECG parameters, including rhythm, ventricular rate, PR interval, QRS duration, QT interval, QTc interval and max QRS amplitude, will be summarized using descriptive statistics at each visit. An overall interpretation of the ECG at each visit will be summarized by displaying the frequency (percentage) of results in each category (categories: no significant change from Baseline ECG, clinically significant change from baseline or not applicable). An outlier analysis will be performed for corrected QT interval (Bazett and Fridericia). This summary will include the number and percentage of patients with post-baseline corrected QT intervals in various categories. Clinically significant changes from baseline in these parameters will be presented in a separate by-patient listing.

Prior and Concomitant Medications: Prior and concomitant medications will be tabulated by Anatomic Therapeutic Class (ATC) and Preferred Term and by overall decreasing frequency of patients who took the medications. Details of prior and concomitant medications will be presented by-patient in a data listing.

Ophthalmic Exam and Slit lamp: An ophthalmic exam will be conducted in addition to a slit lamp examination. For each eye and eye structure (iris, conjunctiva, anterior chamber, iris, lens,

and lid), the frequency (percentage) of patients reporting Normal, Abnormal (not clinically significant [NCS]), Abnormal (clinically significant [CS]) results will be presented. An overall frequency of the change in status from baseline (unchanged, worsened, improved) will be summarized by visit.

Events of Interest:

Injection Site Reactions (ISRs): Tabular summaries of frequency (percentage) of ISRs by SOC and PT will be generated for all events and by time period (eg, loading dose, every 6 months). See Appendix 4. These analyses may be produced for all ISRs by maximum severity and ISRs by severity as well as other subgroups. In addition to summaries of frequencies by SOC and PT, frequencies of adverse events may also be summarized by High-Level Group Term (HLGT) or High-Level Term (HLT), as appropriate. Time from first dose of revusiran to first ISR will be analyzed. For patients without an ISR, patients will be censored at the last day on study.

Liver Function Tests (LFTs): Plots displaying the distribution of the result and ratio of result/threshold at each visit will also be produced. Threshold value (eg, 2×ULN, 3×ULN, 5×ULN, etc.) will vary depending upon the clinical laboratory parameter. Plots of concurrent and non-concurrent peak bilirubin versus peak ALT or AST will be presented. Shift tables will also be employed displaying categorical shifts from baseline to maximum post-baseline category (collected using all scheduled and unscheduled visits) for each LFT parameter. Shift tables of will be based grading using CTCAE criteria or DILI guidance (or both). Summaries of time from date of first dose to first result > threshold and total number of results > threshold at each visit will be generated separately for each LFT parameter.

7.3. Secondary Objectives:

- To assess the PD effect of long-term dosing of revusiran on serum levels of TTR

Parameters: PD assessments will examine the impact of revusiran on serum levels of TTR. Serum levels of vitamin A will also be evaluated as a secondary PD biomarker.

Analysis: These analyses will use the PD Analysis Set. Data will be tabulated for all treated patients and also by ATTR diagnosis (familial amyloidotic cardiomyopathy [FAC] vs. senile systemic amyloidosis [SSA]).

PD Parameters: Measurements of each PD parameter (TTR and Vitamin A) will be summarized separately at each scheduled time point using descriptive statistics. Actual values and relative fold values will be summarized in a tabular format. Plots of the group means (±SEM) of actual and relative fold values from baseline to each scheduled visit will be generated. A tabular display of the maximum reduction (nadir) and corresponding visit at the maximum reduction will be displayed along with the group means (±SEM) of the maximum

nadir. Maximum reduction between FAC and SSA populations using a t-test may also be compared. Per-patient plots will be generated.

Our main interest is to explore whether relative fold of the PD parameter changes over time. The following repeated measures ANCOVA model will be explored:

Primary Analysis [All Patients]:

Model: [redacted]

Secondary Analysis [Subset by ATTR diagnosis (FAC, SSA)]:

Model: [redacted]

For each analysis, mean (relative fold) with associated 95% CIs and p-value at each follow-up day will be presented. All the models will assume a covariance structure of autogressive first order (ar[1]). Only measurements collected at scheduled time points will be considered.

We will also calculate the area under the curve (AUC) for each ATTR diagnosis. The trapezoidal rule will be used to approximate the AUC. The span of time that will be estimated will start at baseline (time=0) and end at the last scheduled collection for each patient. Only scheduled assessments will be considered when calculating the AUC. Patients who discontinued prematurely from the study will have their last PD value carried forward to impute all subsequent visits.

Exploratory Analyses of PD Parameters:

- Differences in relative fold of the PD parameter between ATTR diagnosis (FAC vs. SSA) at each visit may be explored. For that exploratory analysis, the primary model will be used with an additional interaction term of ATTR Diagnosis and visit day.
- Differences in AUC between ATTR diagnosis (FAC, SSA) may be explored using an analysis of covariance (ANCOVA) model where ATTR Type (FAC, SSA) and baseline PD value are covariates in the model.
- Correlations of actual values or changes in actual value between PD parameters vs. clinical outcomes (eg, 6-MWD, EQ-5D, etc..) may be examined. R-square values with the associated 95% confidence interval (CI) around the r-square value and p-values will be generated using either Pearson or Spearman correlation (depending on linearity).

Secondary Objectives (continued):

- To assess clinical effects of long-term dosing of REVUSIRAN, including effect on mortality, hospitalizations, and 6-MWD

Parameters: Assessments of mortality, hospitalizations, and 6-MWD will be examined.

Analysis: These analyses will use the Safety Analysis Data Set. Data will be analyzed for all treated patients in this study and separately by ATTR diagnosis (FAC vs. SSA).

Hospitalizations and Mortality Events: Hospitalizations and mortality events will be summarized separately by classification (cardiovascular [CV] events, heart failure [HF] events and all events [pooling CV and HF]). Classifications for CV and HF events will be provided to Alnylam by Cardiovascular Clinical Studies (an independent committee which will classify the type of hospitalizations and death).

To understand the frequencies and occurrences of these events, the following analyses will be conducted:

1. Generate distribution of time (months) from first dose of revusiran to first event using Kaplan-Meier Method. Time to event and associated 95% confidence interval will be presented at percentiles using Brookmeyer-Crowley methodology. Any patient who does not meet the event criteria will be censored at the last date on the study
2. Calculate the number (percentages) of patients with an event at visit intervals and calculate the cumulative number (percentages) of patients that experienced at least one event up to visit intervals [visits intervals: 0 to ≤ 6months, >6 to ≤12 months, >12-≤18 months, >18 -≤24 months]
3. Calculate the total number of events per patient reported during visit intervals [visit intervals 0 to ≤6 months, >6 to ≤ 12 months, >12 to ≤ 18 months and >18 to ≤24 months]

6MW-D: The main interest of this study will be focused on changes in 6-MWD over time. The following repeated measures ANCOVA model will be explored:

Primary Analysis [All Patients]:

Model: [redacted]

Secondary Analysis [Subset by ATTR diagnosis (FAC, SSA)]:

Model: [redacted]

For each analysis, mean change in 6-MWD (meters) with associated 95% CIs will be presented at each follow-up month. Additional inferential testing may be done. All the models will assume a covariance structure of autogressive first order (ar[1]). Only measurements collected at scheduled time points will be considered.

Descriptive statistics of the actual distance (meters), change in actual distance (meters) from baseline (meters) and percent change from baseline (%) at each visit will be generated. Graphics of the group means (± SEM) and per-patient graphics will also be produced.

For all these 6-MWD analyses, we will generate summaries using 2 datasets:

- Dataset where we only include result where the patient did not worsen from baseline in terms of walking aids needed and/or flow rate of oxygen.
- Dataset where all post-baseline data regardless of conditions (eg, if the patient needed a walking aid during a follow-up, which was not present prior to the first dose of revusiran, then the measurement will be included in the analysis).

Frequencies (percentages) of characteristics of 6-MWD will be summarized by visits (eg, number of patients who did not have the ability to continue to walk at the visit, patients who needed to use a walking aid [and reason why they needed a walking aid]).

7.4. Tertiary Objectives:

- To further characterize the PK of revusiran

Analysis: PK analyses are outside the scope of this document.

- To assess the clinical effects of revusiran

Parameters: Clinical effect parameters include ECHO (Appendix 1), cardiac biomarkers (NT-proBNP and troponin T and I), quantification of fat pad aspirates, CMR (Appendix 2), KCCQ, ^{99m}Tc imaging, eGFR, NYHA class, mBMI , new onset or recurrence of atrial fibrillation, pacemaker placement, change in diuretic regimen, and EQ-5D QOL questionnaire.

Analysis: These analyses will use the Safety Analysis Data Set. Data will be tabulated for all treated patients and by ATTR diagnosis (FAC vs. SSA).

Clinical Parameters: For clinical effect parameters that are continuous descriptive statistics will be provided. Tabular summaries of actual value, change from baseline, and percent change from baseline at each visit will be presented. Graphics of the group means (±SEM) and per-patient graphics will be generated.

The following repeated measures ANCOVA model will be explored:

Primary Analysis [All Patients]:

Model: [redacted]

Secondary Analysis [Subset by ATTR diagnosis (FAC, SSA)]:

Model: [redacted]

For each analysis, mean change with associated 95% CIs at each follow-up day will be presented. Additional inferential testing may be done. All the models will assume a covariance structure of autogressive first order (ar[1]). Only measurements collected at scheduled time points will be considered.

For clinical effect parameters, which are categorical in nature, frequencies (percentage) from baseline to each post-baseline visit will be presented. Categorical shifts from baseline to worst-post-baseline shift will also be presented. Additional inferential testing may be done.

Additional details regarding selected Clinical Parameters:

EQ-5D: EQ-5D measurements will be summarized for each of the 5 domains and total health today score at each visit using descriptive statistics. To calculate the EQ-5D index score based on the 5 domains, the United States will be used as a reference country.

KCCQ: For KCCQ, each question will be scored by assigning each response an ordinal value where a value of 1 represents the lowest level of functioning. The following descriptions provide the details of how the KCCQ domain scores are derived. The descriptions are based on a validated SAS program provided by the organization in charge of the licensing of KCCQ use:

[redacted]

New or recurrent atrial fibrillation: The number and associated percentage of patients with a new onset or recurrence of atrial fibrillation will be summarized overall and every 6 months (depending on the number of events). To determine if a prior occurrence of atrial fibrillation existed, a medical review will be conducted of the medical history for each patient to determine if a prior event existed. Atrial fibrillations on study treatment will be defined as an event which was classified as treatment-emergent atrial fibrillation. Time from first dose of revusiran in this study to event analyses may be considered depending on the number of events. These analyses will be performed using Kaplan-Meier method. The median and associated 95% CIs of the median will be obtained using Brookmeyer-Crowley methodology.

Changes in diuretic regimen: Analyses for change in diuretic regimen will be summarized in the same manner as atrial fibrillation analyses. Any medication classified with ATC classification "C03C" based on the World Health Organization Drug Dictionary are considered diuretics. A medical review will be conducted of all patients reporting diuretic use prior and on-study treatment to determine the number of patients who reported any change and analyses may also be focused upon specific changes in dosage, medication, frequency, etc.

The overall number of patients (percentages) reporting a pacemaker placement on study will be reported.

Tertiary Objectives (continued):

- To understand disease burden and health care utilization.

Parameters: A pharmacoeconomics questionnaire will be used to understand disease burden and health care utilization.

Analysis: These analyses will use the Safety Analysis set. Data will be tabulated for all treated patients and by ATTR diagnosis (FAC vs. SSA).

Frequencies (and associated percentages) will be tabulated to understand symptoms of the patients, understand the employment history and current employment status of the patient and caregiver. These summaries will be generated at each of the scheduled visits.

8. CHANGES TO PLANNED ANALYSES FROM PROTOCOL

The analyses presented in this analysis plan are consistent with those described in the study protocol.

Appendix 1: Selected Echocardiographic Parameters

Please refer to Cardiac Imaging Core Lab - Data Management Plan for details.

Parameter	Unit
Interventricular septum thickness	cm
Left ventricular mass	g
Mean left ventricular wall thickness	cm
Cardiac output	l/min
Lateral early diastolic myocardial velocity	cm/sec
E/Em lateral ratio	
Average peak longitudinal strain	%
Average peak circumferential strain	%
Left ventricular ejection fraction	%
Left atrial volume	mL

Appendix 2: Selected Cardiac Magnetic Resonance Imaging Parameters

Please refer to Cardiac Imaging Core Lab - Data Management Plan for details.

Parameter	Unit
Left atrial volume	ml
Left ventricular end-diastolic volume	ml
Left ventricular end-diastolic volume index	ml/m^2
Left ventricular end-systolic volume	ml
Left ventricular end-systolic volume index	ml/m^2
Left ventricular ejection fraction	%
Left ventricular mass	g
Global myocardial extracellular volume fraction	
Average myocardial extracellular volume fraction - apical	
Average myocardial extracellular volume fraction - basal	
Average myocardial extracellular volume fraction - mid-section	

Appendix 3: Selected Clinical Laboratory Evaluation Parameters

Hematology	
Hematocrit	Neutrophils, absolute and %
Hemoglobin	Lymphocytes, absolute and %
Red blood cell (RBC) count	Monocytes, absolute and %
White blood cell (WBC) count	Eosinophils, absolute and %
Mean corpuscular volume	Basophils, absolute and %
Mean corpuscular hemoglobin	Platelet count
Mean corpuscular hemoglobin concentration	
Serum Chemistry	
Sodium	Phosphate
Potassium	Albumin
Blood urea nitrogen (BUN)	Calcium
Creatinine	Carbon dioxide
Uric acid	Chloride
Lactate dehydrogenase (LDH)	
Glucose	
Liver Function Tests	
Aspartate transaminase (AST)	Alkaline phosphatase (ALP)
Alanine transaminase (ALT)	Bilirubin (total and direct)
Coagulation Studies (in patients taking anticoagulants only)	
Prothrombin time (PT)	International Normalized Ratio (INR)
Activated partial thromboplastin time (aPTT)	
Thyroid Function Test	
Thyroid stimulating hormone (TSH)	
Urinalysis	
pH (dipstick)	Bilirubin
Specific gravity	Nitrite
Ketones	Red blood cells
Protein	Urobilinogen
Glucose	Leukocytes

Appendix 4: Preferred Terms: Injection Site Reactions [ISRs]

Code	Term	Level
10058729	Embolia cutis medicamentosa	PT
10057664	Injected limb mobility decreased	PT
10022044	Injection site abscess	PT
10022045	Injection site abscess sterile	PT
10022046	Injection site anaesthesia	PT
10022048	Injection site atrophy	PT
10054812	Injection site calcification	PT
10050057	Injection site cellulitis	PT
10050082	Injection site coldness	PT
10022055	Injection site cyst	PT
10022056	Injection site dermatitis	PT
10065600	Injection site discharge	PT
10051572	Injection site discolouration	PT
10054266	Injection site discomfort	PT
10067252	Injection site dryness	PT
10069124	Injection site dysaesthesia	PT
10066221	Injection site eczema	PT
10022059	Injection site erosion	PT
10022061	Injection site erythema	PT
10068689	Injection site exfoliation	PT
10022062	Injection site extravasation	PT
10022064	Injection site fibrosis	PT
10022065	Injection site granuloma	PT
10022066	Injection site haematoma	PT
10022067	Injection site haemorrhage	PT
10022071	Injection site hypersensitivity	PT
10022072	Injection site hypertrophy	PT
10022075	Injection site induration	PT
10022076	Injection site infection	PT
10022078	Injection site inflammation	PT
10066083	Injection site injury	PT
10022079	Injection site irritation	PT
10048648	Injection site ischaemia	PT
10064494	Injection site joint effusion	PT
10064111	Injection site joint inflammation	PT
10053979	Injection site joint movement impairment	PT
10049261	Injection site joint pain	PT
10049263	Injection site joint redness	PT
10049260	Injection site joint swelling	PT

10049262	Injection site joint warmth	PT
10067253	Injection site laceration	PT
10057665	Injection site lymphadenopathy	PT
10067255	Injection site macule	PT
10022081	Injection site mass	PT
10056250	Injection site movement impairment	PT
10022082	Injection site necrosis	PT
10022083	Injection site nerve damage	PT
10057880	Injection site nodule	PT
10022085	Injection site oedema	PT
10022086	Injection site pain	PT
10066041	Injection site pallor	PT
10066044	Injection site papule	PT
10022088	Injection site paraesthesia	PT
10022090	Injection site phlebitis	PT
10053396	Injection site photosensitivity reaction	PT
10022093	Injection site pruritus	PT
10054994	Injection site pustule	PT
10022094	Injection site rash	PT
10022095	Injection site reaction	PT
10066797	Injection site recall reaction	PT
10066210	Injection site scab	PT
10059009	Injection site scar	PT
10066778	Injection site streaking	PT
10053425	Injection site swelling	PT
10022104	Injection site thrombosis	PT
10022105	Injection site ulcer	PT
10022107	Injection site urticaria	PT
10067995	Injection site vasculitis	PT
10022111	Injection site vesicles	PT
10022112	Injection site warmth	PT
10025478	Malabsorption from injection site	PT

APPENDIX 5: VISIT WINDOWS

Planned Visit	Analysis Window
Screening Visit	Prior Visit up to Day -1 before dose
Pre-Dose	Day 0 (collected prior to dose)
Day 0 (first dose)	Day 0 (on or after first dose)
Day 1	Day 1
Day 2	Day 2
Day 3	Day 3
Day 4	Day 4
Day 7	Day 6 to Day 8
Day 84/Month 3	Day 70 to Day 98
Day 168/Month 6	Day 154 to Day 182
Day 252/Month 9	Day 238 to Day 266
Day 336/Month 12	Day 322 to Day 350
Day 420/Month 15	Day 406 to Day 434
Day 504/Month 18	Day 490 to Day 518
Day 588/Month 21	Day 574 to Day 602
Day 672/Month 24 (End of Treatment*)	Day 665 to Day 679
Follow-up (Day 700) for patients who premature discontinued from study	No window

Definitions:

Relative Month=(date of visit – date of first dose+1)/30.4

Relative Day=(date of visit – date of first dose+1)

Notes:

a) If there are multiple assessments during a planned visit, the assessment closest to the planned visit will be selected. If the 2 assessments are equidistant from the window then the assessment prior to the planned visit will be selected.
b) Patients who prematurely discontinue study will not have their data combined with patients who completed an assessment for planned visit =Day 672 for aggregated summaries (eg, group means).
c) Per patient listings/plots for safety labs will be plotted by relative day/month from first dose (including scheduled and unscheduled visits). Per subject listing/plots for efficacy or PD parameters will be plotted by planned visits using only scheduled time points (note: planned visit does not include early termination or follow-up).
d) Summary statistics (eg, group Means) plots will be plotted by planned visits using only scheduled visits.

APPENDIX 6: KCCQ DERIVATIONS

Physical Limitation (PL)

[redacted]

Symptom Stability (SS)

[redacted]

Symptom Frequency (SF)

[redacted]

Symptom Frequency (SF)

[redacted]

Symptom Burden (SB)

[redacted]

Total Symptom Score (TS)

[redacted]

Self-Efficacy (SE)

[redacted]

Quality of Life (QL)

[redacted]

Social Limitation (SL)

[redacted]

[redacted]