Alnylam Pharmaceuticals

Protocol No.: ALN-TTRSC-004

A Phase 3 Multicenter, Multinational, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ALN-TTRSC in Patients with Transthyretin (TTR) Mediated Familial Amyloidotic Cardiomyopathy (FAC)

STATISTICAL ANALYSIS PLAN

Version: 1.0
Date of Issue: 21 October 2015

Alnylam Pharmaceuticals, Inc.
300 Third Street
Cambridge, MA 02142

APPROVALS

The undersigned agree that all required reviews of this document are complete, and approve this Statistical Analysis Plan as final.

[redacted] **Approval:**

Signature Date

[redacted] Senior Manager, Biostatistics
Printed Name/Title

Signature Date

[redacted] Senior Manager, Health Economics and Outcomes Research
Printed Name/Title

Alnylam Approval:

[redacted] 21 OCT 2015
Signature Date

[redacted] Senior Manager, Biostatistics
Printed Name/Title

[redacted] 28 OCT 2015
Signature Date

[redacted].; Senior Director, Biometrics
Printed Name/Title

[redacted] 27 Oct 2015
Signature Date

[redacted] Senior Director, Clinical Development
Printed Name/Title

[redacted] 28 oct 2015
Signature Date

[redacted] Senior Vice President, Clinical Development
Printed Name/Title

APPROVALS

The undersigned agree that all required reviews of this document are complete, and approve this Statistical Analysis Plan as final.

[redacted] **Approval:**

[redacted] 27 Oct 2015

Signature Date

[redacted] Senior Manager, Biostatistics

Printed Name/Title

Signature Date

[redacted] Senior Manager, Health Economics and Outcomes Research

Printed Name/Title

Alnylam Approval:

Signature Date

[redacted] MA; Senior Manager, Biostatistics

Printed Name/Title

Signature Date

[redacted] Senior Director, Biometrics

Printed Name/Title

Signature Date

[redacted] Senior Director, Clinical Development

Printed Name/Title

Signature Date

[redacted] Senior Vice President, Clinical Development

Printed Name/Title

APPROVALS

The undersigned agree that all required reviews of this document are complete, and approve this Statistical Analysis Plan as final.

[redacted] **Approval:**

Signature Date

[redacted] Senior Manager, Biostatistics
Printed Name/Title

[redacted] Oct 27th 2015
Signature Date

[redacted] Senior Manager, Health Economics and Outcomes Research
Printed Name/Title

Alnylam Approval:

Signature Date

[redacted] Senior Manager, Biostatistics
Printed Name/Title

Signature Date

[redacted] Senior Director, Biometrics
Printed Name/Title

Signature Date

[redacted] Senior Director, Clinical Development
Printed Name/Title

Signature Date

[redacted] Senior Vice President, Clinical Development
Printed Name/Title

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
6-MWD	Six-minute walk distance
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
ANCOVA	Analysis of covariance
BMI	Body mass index
bpm	Beats per minute
EQ-5D-5L	EuroQoL 5 Domains, 5 Levels of response
CAC	Clinical Adjudication Committee
CMR	Cardiac magnetic resonance imaging (Cardiac MRI)
CV	Cardiovascular
DMC	Data Monitoring Committee
eAUC	Area under the effect curve
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
FAC	Familial amyloidotic cardiomyopathy
HF	Heart failure
HR	Heart rate
ISR	Injection site reaction
KCCQ	Kansas City Cardiomyopathy Questionnaire
KM	Kaplan-Meier
MAR	Missing At Random
mBMI	Modified body mass index
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
MMRM	Mixed-effects model repeated measures
NT proBNP	N-terminal prohormone of B-type natriuretic peptide
NYHA	New York Heart Association
PEQ	Pharmacoeconomics Questionnaire
PK	Pharmacokinetic(s)
PND	Polyneuropathy Disability
PP	Per protocol
PRO	Patient Reported Outcome
PT	Preferred term
QTcB	Bazett-corrected QT interval
QTcF	Fridericia-corrected QT interval
RBP	Retinol binding protein
SAE	Serious adverse event
SAP	Statistical Analysis Plan

SD	Standard deviation
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TTR	Transthyretin
ULN	Upper limit of normal

1 SOURCE DOCUMENTS

The Statistical Analysis Plan (SAP) was written based on the following documentation:

Document	Date	Version
Protocol	03 October 2014	1.0
CRF	02 June 2015	6.0

2 PROTOCOL DETAILS

2.1 Study Objectives

The primary objective of the study is to determine the efficacy of ALN-TTRSC (referred to as revusiran hereafter) in patients with familial amyloidotic cardiomyopathy (FAC).

The primary objective will be assessed as the difference between revusiran and placebo groups at 18 months for co-primary endpoints of (1) change in 6-minute walk distance (6-MWD) from baseline (meters); and (2) percentage reduction in serum transthyretin (TTR) levels from baseline.

2.2 Overall Study Design

This is a multicenter, multinational, randomized, double-blind, placebo-controlled Phase 3 study designed to demonstrate the clinical efficacy and safety of revusiran in patients with TTR mediated FAC.

Approximately 200 consented patients will be randomized to receive either revusiran or placebo at a 2:1 ratio (revusiran to placebo) in a blinded manner as a subcutaneous administration. Treatment groups will be balanced at randomization for NYHA classification (levels: I and II versus III), TTR mutation [redacted] and 6-MWD [redacted]. Patients will receive revusiran or placebo daily for 5 days after being randomized, a single dose on Day 7, and then weekly for 18 months.

Patients will undergo scheduled efficacy and safety assessments prior to study drug (Screening/Pre-dose), every month for the first 3 months from day of first dose of study drug, and then at 3-6 month intervals thereafter. Full details of the clinical assessments can be found in the protocol.

An independent Clinical Adjudication Committee (CAC) will adjudicate the secondary endpoints of mortality and hospitalization.

A Data Monitoring Committee (DMC) will be established for the study and operate under a pre-specified charter.

2.3 Sample Size and Power

For the 6-MWD primary endpoint, a sample size of 180 with a 2:1 treatment allocation (N=120 on revusiran and N=60 on placebo) has approximately 90% power to detect a treatment difference of 0.55 standard deviations using a Finkelstein and Schoenfeld analysis with a two-sided significance level of 0.05. This assumes that 20% of placebo patients and 13% of revusiran patients will die before the 18 month assessment (ie, hazard ratio = 0.6). Assuming a standard deviation of 70 meters in change from baseline, this would correspond to approximately 90% power to detect a treatment effect of 39 meters in the 6-MWD. Assuming a 10% patient dropout rate, approximately 200 patients will be enrolled in the study. Note that power for the comparison of percent reduction in serum TTR between treatment groups is expected to be >90% for a significance level of 0.05; sustained knockdown of serum TTR levels

>85% has been observed in healthy volunteers and patients receiving revusiran. For this reason, the overall power to establish efficacy is expected to be approximately 90% under the assumptions described above.

3 EFFICACY AND SAFETY VARIABLES

3.1 Primary Efficacy Endpoints

The co-primary endpoints are to evaluate differences between revusiran and placebo for:

- Change in 6-MWD (meters) from baseline to 18 months
- Percentage reduction in serum TTR burden from baseline over 18 months

3.2 Secondary Efficacy Endpoints

The secondary endpoints are to evaluate differences between revusiran and placebo at 18 months for:

- Composite Cardiovascular (CV) mortality and CV hospitalization
- Change from baseline in New York Heart Association (NYHA) class
- Change from baseline in Kansas City Cardiomyopathy Questionnaire (KCCQ) - Overall Summary Score
- CV mortality
- CV hospitalization
- All-cause mortality

3.3 Exploratory Efficacy Endpoints

The exploratory endpoints of the study are to evaluate differences between revusiran and placebo at 18 months for:

- EuroQoL 5 Domains, 5 Levels of response (EQ-5D-5L) questionnaire
- Echocardiogram (ECHO) parameters
- Karnofsky Performance Status
- Troponin T and I, and N-terminal prohormone of B-type natriuretic peptide (NT proBNP) levels
- Cardiac magnetic resonance imaging (CMR) parameters (only at selected sites)
- Technetium-99m scintigraphy parameters (only at selected sites)
- Amyloid in abdominal wall fat pad aspirates
- Polyneuropathy Disability (PND) Score
- Modified body mass index (mBMI)
- Estimated glomerular filtration rate (eGFR)
- Heart Failure (HF) hospitalization

3.4 Safety Variables

Safety will be assessed throughout the study by collecting the following measurements:

- Adverse events (AEs; including serious adverse events [SAEs])
- Concomitant Medications
- Clinical laboratory safety tests including hematology, serum chemistry (including liver function tests), thyroid function, coagulation, vitamin A, and urinalysis
- Anti-drug antibodies
- Electrocardiograms (ECG)
- Vital signs and body weight
- Physical examination findings
- Ophthalmology examinations

3.5 Other Variables

- Disease burden and health care utilization will be assessed using a patient reported pharmacoeconomics questionnaire

4 PHARMACOKINETIC/PHARMACODYNAMIC VARIABLES

Pharmacokinetics (PK) will be assessed by collecting periodic plasma samples. Analysis of PKPD parameters will be described in a separate document.

5 ANALYSIS POPULATIONS

5.1 Modified Intent-to-Treat

The modified Intent-to-Treat (mITT) population will be defined as all randomized patients who received at least 1 dose of revusiran or placebo.

5.2 Safety

The safety population will be defined as all patients who received at least 1 dose of revusiran or placebo.

5.3 Per-Protocol

The Per-Protocol (PP) population will be defined as all patients who did not have any major protocol deviations (see Section 5.3.1), and completed the 18 month 6-MWD assessment or died on-study prior to Month 18 analysis visit.

Major protocol deviations leading to exclusion from PP analysis are detailed in Section 5.3.1.

The primary analysis population for efficacy analyses (including co-primary and secondary endpoints) will be the mITT population. As a sensitivity analysis, the co-primary endpoints will also be analyzed using the PP population. All efficacy analyses will be analyzed with patients grouped by the treatment to which they were randomized.

The primary analysis population for safety analyses will be the safety population, and all safety analyses will be analyzed by the treatment that was actually received. If a patient received at least one dose of revusiran, he/she would be grouped in the revusiran arm for safety analyses.

5.3.1 Protocol Deviations Leading to Exclusion from the PP Analysis

Major protocol deviations leading to exclusion from the PP analysis will be reviewed and approved by Alnylam prior to database lock and unblinding of treatment assignments for all patients. This document of all major deviations will include a description of the deviation and the reason that the deviation demonstrates the need to exclude the patient from the PP population. Additional important protocol deviations leading to exclusion from the PP population may be identified during the study. The final document of major deviations will be finalized prior to database lock and unblinding of the treatment assignments for all patients.

The major protocol deviations leading to exclusion from PP population will be summarized by treatment group, and presented in a data listing.

At a minimum, the following criteria have been identified a priori as critical protocol deviations that will impact the co-primary efficacy endpoints and require exclusion from the PP population:

- Failure to meet one or more of the key inclusion/exclusion criteria (listed below)
- Receiving incorrect study drug for ≥1 administration
- Receiving <80% of scheduled doses or missed ≥ 6 consecutive doses

Key inclusion criteria:

1. Have a documented TTR mutation
2. Amyloid deposit in cardiac or non-cardiac tissue confirmed by Congo Red staining
3. Have a history of heart failure (HF) with at least 1 prior hospitalization for HF OR clinical evidence of HF that either requires/required diuretics or is/was associated with an NT-proBNP>400 ng/L or BNP >100 ng/L
4. Have evidence of cardiac involvement by Screening/Baseline echocardiogram including an end-diastolic intraventricular septum thickness of ≥ 12 mm. For patients with an end-diastolic intraventricular septum thickness of < 12 mm, an endomyocardial biopsy showing amyloid deposition is required.
5. Can walk ≥ 150 meters on a 6-MWD test
6. Have a Karnofsky performance status of ≥ 50%

Key exclusion criteria:

1. Has known primary amyloidosis (AL), leptomeningeal amyloidosis, non-FAC hereditary cardiomyopathy, hypertensive cardiomyopathy or cardiomyopathy due to valvular heart disease.
2. Had a known peripheral vascular disease affecting amubulation
3. Had an acute coronary syndrome within the past 3 months.
4. Has a PND score>2
5. Has an NYHA classification of IV
6. Has received an investigational agent or device within 30 days of anticipated study drug administration or 5 half-lives of the investigational drug, whichever is longer.

7. Is currently taking diflunisal, tafamidis, doxycycline, or tauroursodeoxycholic acid; if previously on any of these agents, must have completed the 14-day wash-out prior to start of study drug administration.

6 DATA HANDLING

6.1 Time Points and Visit Windows

Day 1 will be defined as the day of first dose of study drug.

An evaluation date will be calculated relative to Day1 as follows:

- RelDay = (date of assessment – date of first dose + 1) if collected after Day 1.
- RelDay = (date of assessment – date of first dose) if collected prior to Day 1.

For analysis by visit, analysis windowing will be utilized for each scheduled visit such that unscheduled visits will also be considered. If there is more than one value within a visit window then the visit closest to the target day of the visit will be used in the analysis. If measurements are equally distant to the target day, then the later one will be used in the analysis. Details regarding the definition of the visit window will be summarized in a separate specifications document.

Baseline Definitions:

- For 6-MWD, baseline will be defined as the latest value prior to the first dose. If Day 1 assessment is not available, then the latest of the 2 screening 6MWD results will be selected to represent the baseline value for the patient in the analysis.
- For each of the PD parameters, baseline will be defined as the average of all measurements collected prior to the date of the first dose of study drug.
- For all other parameters, the baseline will be defined as the last assessment prior to the first dose of study drug.

6.2 Handling of Dropouts or Missing Data

6.2.1 Efficacy Analysis

Patients who discontinue study drug prior to Month 18 will be encouraged to remain on the study and complete their remaining clinic visits through the 18-month visit. However it is possible that data will remain missing.

For the primary analysis of the co-primary efficacy endpoints, imputation of data will be performed if such cases occur:

- For calculation of eAUC (serum TTR), any assessment missing due to death or treatment discontinuation will be imputed using the baseline value, and thus the percent change at the visit will be 0%.
- If the serum TTR is recorded as "< value" then it will be imputed as half of that value (eg, TTR < 8.16 ng/mL will be imputed to be a value of 4.08).

For the primary analysis of the secondary efficacy endpoints, imputation of missing data will be performed if such cases occur:

- In the rare event that hospitalization dates are partially missing, imputation will be performed using the same approach as partial AE start dates (see Section 6.2.2).
- For KCCQ, missing responses to specific items will be handled in a manner consistent with standard patient reported outcome (PRO) scoring algorithms: a 50% proration rule will be applied to PRO data at the item level. Specifically, patients have to complete a minimum of half of the total number of items in each subscale to receive a valid subscale score; otherwise the subscale will not be scored. Missing scores at subscale level will not be imputed. Details of KCCQ scoring are described in Appendix III.

6.2.2 Safety Analysis

All safety analyses will be performed on observed data only. No missing data will be imputed except for partial dates of adverse events (AE) and concomitant medications (note: missing time will not be imputed).

Imputation rules for End Date of AE:

- If end date is completely missing, then end date remains missing (assume ongoing event)
- For a partial End date (day is missing, or month is missing or both day and month are missing) then the last day/month will be imputed.

Imputation rules for Start Date of AE:

- If start date is completely missing, then start date will be imputed to be the date of the first dose of study drug
- For a partial Start date (day is missing, month is missing or both day and month are missing):
  - partial date < the first dose date: the last day/month

- partial date = the first dose date: the first dose date
- partial date > the first dose date: the first day/month

If the imputed AE start date is after the imputed AE stop date, then the start date will be set to the imputed AE stop date.

For medications with partial start or stop dates: the first day/month will be imputed for start date, and the last day/month will be imputed for stop date.

For mediations with a completely missing start date, the medications will be considered as started prior to the first dose of study drug; medications will be classified as prior or concomitant depending on the medication stop dates. A completely missing stop date of medications will not be imputed and the medications will be assumed as ongoing.

Imputed dates will be used to determine if an adverse event is treatment-emergent, or a medication is a prior or concomitant medication. Imputed dates will not be listed in listings.

7 STATISTICAL METHODS

7.1 General Principles

All data processing, summarization and analyses will be performed using the SAS Version 9.3 (or later) of the SAS® statistical software package.

All data collected will be sorted and presented in listings by treatment group, site, patient identification, assessment, relative day (see Section 6.1 for definition) and visit (where applicable), unless otherwise specified.

Data will be presented in summary tables by treatment group (revusiran, placebo), assessment and visit (where applicable).

Descriptive summary statistics for continuous variables will include the number of patients/observations (N), mean, standard deviation (SD), median and range (minimum, maximum).

Descriptive summary statistics for categorical variables will include frequency counts and percentages for each category [n (%)]. A category of missing will be included if the number missing is greater than zero. Unless stated otherwise in the table shells, the denominator for percentage calculations will be the number of patients in the analysis population.

All statistical tests will be 2-sided and performed at the 5% significance level, unless otherwise specified. Confidence intervals of 95% will be provided where appropriate.

7.2 Subject Disposition and Data Sets Analyzed

Patient disposition will be listed and summarized by treatment group and will include the number and percentage of patients:

- Enrolled (signed informed consent and met eligibility)
- Randomized
- Treated
- mITT population
- Safety population

- Per-Protocol population

Summaries of the number and percentage of patients who completed the study, who completed study treatment, who discontinued study treatment and completed the remainder of required study visits through Month 18, who discontinued study treatment but did not complete the remainder of required study visits, and the primary reasons for study and treatment discontinuation will be presented for all randomized patients.

Descriptive statistics will also be presented for time from first dose of study drug to discontinuation of study treatment (months) and there will be a summary of the number (percentage) of patients who discontinued study treatment at 3 month intervals.

In addition, descriptive statistics of the difference in days from time of randomization to date of first dose of study drug will be provided in a separate table.

A summary of patients randomized by country and site will be provided by treatment group for all patients randomized.

7.3 Protocol Deviations

All protocol deviations leading to exclusion from the PP population (see Section 5.3.1) will be listed and summarized by treatment group for the mITT population. In addition, all protocol deviations (major and minor) will be summarized in a separate listing.

The deviations will be identified before data are unblinded.

7.4 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be listed and summarized by treatment group for mITT and PP analysis populations. Standard descriptive statistics will be presented for the following:

Demographics:

- Age at randomization (years) and Age categories
- Gender
- Race
- Ethnicity
- Regions (North America, Europe, Rest of World)
- Body weight (kg) and categories
- Height (cm)
- BMI (kg/m^2)
- Modified BMI and categories
- Genotype

Stratification factors (note: summarized separately based upon responses in IVRS and eCRF):

- 6-MWD (meters) and 6-MWD categories (≤325 vs. >325 meters)
- TTR mutation categories (V122I, other FAC mutations)
- NYHA categories (I, II vs. III)

Other key baseline disease characteristics:

- Karnofsky Performance Status
- Time from ATTR diagnosis to informed consent (years)
- eGFR
- PND Score

Patients will be categorized in a region based upon the location of the clinical site.

An additional per patient listing will be provided of other screening test results such as Vitamin A, serum protein electrophoresis (SPEP) with immunofixation (IFE), urine SPEP with IFE, and serum free light chain (FLC) and Hepatitis B surface antigens (HBsAg), Hepatitis B surface antibodies (HBsAb) and Anti-hepatitis C virus antibodies (HCV Ab).

7.4.1 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 17.1 or later. All medical history will be provided in a data listing, and the number and percentage of patients with any medical history will be summarized for the mITT analysis population by system organ class (SOC) and preferred term (PT) for each treatment group.

Additional listings will also be provided for any other prior surgeries noted at screening.

7.4.2 Previous and Concomitant Medications

Medications received prior to or concomitantly with study drug will be coded by using the WHO Drug Dictionary Version March 2014 or later.

Prior medications and concomitant medications are defined as follows:

> Prior medications are medications that stopped prior to the first dose of study drug.
>
> Concomitant medications are those with a start date on or after the first dose date of study drug, or those with a start date before the first dose of study drug and are continued after the date of first dose of study drug.

Prior medications, prohibited medications, concomitant medications taken during treatment phase, and medications started after the last dose of study drug will be summarized in a table by ATC classification and preferred term by treatment group.

Prior medications, prohibited medications, and concomitant medications will be provided in data listings.

In addition, a separate listing of diuretic medications prior and concomitant will be generated by treatment group. Any medication classified with ATC classification "C03C" based on the World Health Organization Drug Dictionary are considered diuretic medication.

7.5 Extent of Exposure

Study drug exposure will include descriptive statistics of the duration of treatment (months) and total number of doses of study drug by treatment group. Additional summaries of the cumulative number of patients (percentage) that completed study treatment at visit intervals (e.g. <3 months, 3-6 months) and the number of patients (percentage) that completed study treatment at the latest visit interval will also be displayed by treatment group. The cumulative number of patients (percentage) that received doses in each

interval (e.g. loading dose, <12 doses) and the number of patients (percentage) that completed the total number of doses at the interval will also displayed by treatment group.

7.6 Efficacy

All efficacy analyses will be performed on the mITT population. In addition, the analysis of the co-primary efficacy endpoints will be also be evaluated using the PP population.

Where appropriate, analyses will be stratified based upon a subset of stratification parameters used for randomization: TTR mutation (V122I versus other FAC mutations), and 6-MWD (≤325 meters versus >325 meters). The values of these stratified parameters will be based upon the data entered in the eCRF.

7.6.1 Primary Efficacy Analysis

There are two co-primary efficacy endpoints. The first co-primary endpoint is change in 6-MWD from baseline at 18 months after randomization. The second co-primary endpoint is percent reduction in serum TTR burden over 18 months after randomization.

Efficacy of revusiran will be established if the p-value (2-sided) is ≤0.05 for the primary analysis for each of the co-primary endpoints.

7.6.1.1 Change from Baseline in 6-MWD at Month 18

The primary analysis for change from baseline in 6-MWD at month 18 will be performed using a stratified Finkelstein and Schoenfeld Joint Rank Test.

This test will take into account informative missing-ness due to death or loss of ability to perform 6-MWD up to Month 18. In this stratified non-parametric rank sum analysis, all pairs of patients within a stratum are compared. A patient will be compared with another patient in a step-wise fashion to identify the patient in the pair with the better outcome:

[redacted]

[redacted]

7.6.1.2 Sensitivity Analyses for Change in 6-MWD from Baseline at Month 18

All sensitivity analyses will be analyzed using the mITT population.

Sensitivity #1: Address robustness using a different distributional assumption

A mixed-effects model repeated measures (MMRM) analysis based on the restricted maximum likelihood (REML) method for estimation will be performed for the change in 6-MWD from baseline. The MMRM model dependent variable will be change in 6-MWD from baseline (meters). The model will include the fixed effects of treatment group, visit, treatment group-by-visit interaction term, TTR mutation [redacted] and 6-MWD at Screening [redacted] and baseline 6-MWD-by-visit interaction. An unstructured covariance variance matrix will be used to model the correlation among repeated measurements. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The adjusted mean change in 6-MWD from baseline to each visit for each treatment group and corresponding 95% confidence interval will be displayed. The difference in the adjusted mean change in 6-MWD between treatment groups at each visit and corresponding 95% confidence interval will also be estimated. All post-baseline observations collected and designated to each post-baseline analysis visit will be used in the analysis, including data collected after the discontinuation of study drug. Note that this analysis assumes missing data, including those due to death, are MAR.

Sensitivity #2: Address influence of missing data

Complete Cases (CC) analysis will include all patients with non-missing 6-MWD results at 18 months. An ANCOVA model will be employed where the dependent variable is a change from baseline in 6MWD (meters) to month 18 with a covariate for treatment group. No imputation will be considered.

Below are additional descriptive analyses of each component of the co-primary analysis. These analyses will be unstratifed using the mITT population.

Time to death: The distribution of time from date of first dose of study drug to death for each treatment group will be generated using Kaplan-Meier (KM) plot. For each percentile (25^{th}, 50^{th}, 75^{th}) if reached, an estimate of time of death from date of first dose and the associated 95% confidence intervals using Brookmeyer-Crowley methodology will be presented for each treatment group. The survival rates at 3, 6, 9, 12, 15 and 18 months for each treatment group will also be presented. Appendix I includes additional details regarding the definition for time to death.

Time to loss of ability to perform 6-MWD: Time from date of first dose to loss of ability to perform 6-MWD will be based on months 3, 6, 12 and 18 visits. The frequency and percentage of patients who lose the ability to walk will be presented at each analysis visit by treatment group. The cumulative number of patients and associated percentage in each treatment group who were unable to perform the 6-MWD up to month 18 will also be presented. In addition, there will also be a summary table and listing (overall and by visit) of the number (frequency) of patients that were unable to walk at the visit and the corresponding

reasons why the patient was unable to walk. Appendix I includes additional details regarding definition of time to loss of ability to perform 6-MWD.

Change in 6-MWD from baseline: Descriptive statistics of observed change in 6-MWD (meters) from baseline to analysis visits at 3, 6, 12 and 18 months will be generated. Appendix I includes additional details regarding the definition of change in 6-MWD from baseline.

7.6.1.3 Percent reduction in serum TTR from Baseline over 18 months

The primary analysis for the co-primary endpoint of percent change in TTR from baseline over 18 months will be analyzed using an Analysis of Covariance (ANCOVA) model.

The dependent variable used in the ANCOVA model will be area under the effect curve (eAUC) to quantify the percent reduction in TTR from baseline over 18 months. The covariates used in the model will be treatment group, TTR mutation [redacted] and 6-MWD at Screening [redacted] and baseline TTR serum levels. The difference in the adjusted mean eAUC between treatment groups will also be presented with associated 95% confidence interval. The dependent variable will be log transformed.

Calculation of eAUC will be based on trapezoidal method, where the y-axis is percent reduction in serum TTR and the x-axis is time since first dose of study drug. Assessments missing due to death or discontinuation will be imputed using the baseline value, and thus the percent change will be 0%. The span of time will start at time 0 (baseline) and end at month 18. Only scheduled visits will be included in the calculation of eAUC.

7.6.1.4 Sensitivity Analyses for Percent Reduction in Serum TTR from Baseline over 18 months

Sensitivity #1: Address impact of baseline factors

The eAUC will be analyzed using an unadjusted ANOVA model. The covariates of the model will be treatment group and the dependent variable will be eAUC.

Sensitivity #2: Address robustness using a different distributional assumptions

A mixed-effects model repeated measures (MMRM) analysis based on the restricted maximum likelihood (REML) method for estimation will be performed for relative fold change in serum TTR. The dependent variable will be relative fold change defined as (TTR value at follow-up visit/baseline TTR value). The covariates used in the model will be treatment group, visit, treatment group by visit interaction, TTR mutation [redacted] and 6-MWD at Screening [redacted] and baseline TTR serum levels. The difference in the adjusted mean relative fold change in serum TTR between treatment groups and associated 95% will also be presented. The dependent variable will be log transformed.

Sensitivity #3: Address influence of missing data

Complete Cases (CC) analysis will include all patients with non-missing TTR results at month 18. The mixed-effect model used in the sensitivity #2 will be employed. No imputation will be considered. The dependent variable will be log transformed.

Below are additional descriptive analyses of serum TTR. These analyses will be unstratifed using the mITT population.

Serum TTR: Descriptive statistics of serum TTR values, change from baseline in serum TTR values and percent reduction in TTR values will be presented for each treatment group. An additional summary table of descriptive statistics for the maximum percentage reduction in TTR for each treatment group will also be presented.

7.6.1.5 Subgroup Analysis

Subgroup analyses for co-primary endpoints will be performed using mITT population in the following subgroups, defined based on the baseline values:

- Age [<65 at randomization ; ≥65 years at randomization]
- Gender [M; F]
- Race [White; Non-White]
- Region [North America; Europe; Rest of World]
- 6-MWD* [redacted]
- TTR mutation* [redacted]
- NYHA class* [I and II; III] at stratification*
- PND score [0; I; II]

*Categorization of stratification factors (6-MWD, TTR mutation and NYHA class) will use the values from eCRF. Patients will be categorized into a region based upon the location of the site.

Subgroups with > 2 levels may be collapsed due to sparse data at a level prior to unblinding and database lock. The decision to collapse will be justified and documented prior to unblinding.

An unstratified Finkelstein and Schoenfeld Joint Rank Test will be used for the co-primary endpoint of 6-MWD within each subgroup. An ANCOVA model will be used for the co-primary endpoint of percent reduction in serum TTR burden from baseline over 18 months within each subgroup. Covariates include treatment group and baseline TTR in the model.

7.6.2 Secondary Efficacy Analysis

Analyses will be performed in the mITT population for all secondary efficacy endpoints. Type I error control for secondary endpoints will be achieved by the following pre-specified hierarchical order:

- Composite CV mortality and CV hospitalization
- Change from baseline in NYHA class
- Change from baseline in KCCQ - Overall Summary Score
- CV mortality
- CV hospitalization
- All-cause mortality

If and only if a comparison of treatment group is significant ($p \leq 0.05$), then the next endpoint in the

hierarchy may be formally tested.

The classification of mortality and hospitalization events will be determined by an independent Clinical Adjudication Committee (CAC).

7.6.2.1 Composite CV Mortality and CV Hospitalization

The primary analysis of the composite of CV mortality and CV hospitalization will be based on stratified Finkelstein and Schoenfeld Joint Rank Test. All pairs of patients will be compared within a stratum. A patient will be compared with another patient in a step-wise fashion to identify the patient in the pair with the better outcome:

Step 1: Compare time to CV mortality;
If it cannot be determined which patient died earlier due to CV mortality, then go to Step 2

Step 2: Compare number of CV hospitalizations at the latest common study visit

Details of the comparisons of time to CV death and number of CV hospitalizations are described in Appendix I.

Additional descriptive analyses for each component by treatment group will be generated. The number of patients (%) with a CV mortality event will be present at each visit interval [>-0- ≤6 months, >6- ≤12 months, >12-≤18 months and >0-≤18 months].

The cumulative number of CV hospitalizations per patient reported during each visit intervals [>0 to ≤ 6 months, >6 to ≤ 12 months or >12 to ≤ 18 months and >0 to ≤18 months] will be presented for each treatment group. Additionally, at each visit interval, the cumulative number of CV hospitalizations and percentage of patients with a CV hospitalization event will be tabulated.

7.6.2.2 Change in NYHA from Baseline

The primary analysis of change in NYHA from baseline will be based on stratified Finkelstein and Schoenfeld Joint Rank Test. All pairs of patients will be compared within a stratum. A patient will be compared with another patient in a step-wise fashion to identify the patient in the pair with the better outcome:

Step 1: Compare time to death;
If it cannot be determined which patient lived longer, then go to Step 2

Step 2: Compare change in NYHA from baseline to the latest common study visit

Details of the comparisons of time to death and change in NYHA are described in Appendix I.

Descriptive statistics displaying a shift table of baseline NYHA class category [range: 1-4] to each post-baseline visit categories [range: 1-4] will be generated. An overall shift of the baseline to worst post-baseline NYHA class category will be presented as well for each treatment group.

7.6.2.3 Change in overall summary score from Baseline – KCCQ

The primary analysis of change in overall summary score from baseline will be based on stratified Finkelstein and Schoenfeld Joint Rank Test. All pairs of patients will be compared within a stratum. A patient will be compared with another patient in a step-wise fashion to identify the patient in the pair with the better outcome:

Step 1: Compare time to death;

If it cannot be determined which patient lived longer, then go to Step 2

Step 2: Compare change in overall summary score at the latest common study visit

Note: The overall summary score is calculated based on responses from the KCCQ questionnaire. The questionnaire summarizes 8 subscales and 2 summary scores (see Appendix III for further details).

Details of the comparisons of time to death and change in overall summary score are described in Appendix I.

Descriptive statistics of overall summary score and change in overall summary score will be generated for each treatment group at baseline and each post-baseline visit. These analyses above will be repeated for each of the 8 subscales and clinical summary score used in the KCCQ questionnaire.

7.6.2.4 CV Mortality

The primary analysis for time from date of first dose of study drug to CV mortality event will be based upon a stratified log-rank test to compare treatment groups. Definition details for CV mortality are located in Appendix I.

The distribution of time from date of first dose of study drug to CV mortality for each treatment group will be generated using Kaplan-Meier (KM) plot. For each percentile (25^{th}, 50^{th}, 75^{th}) if reached, an estimate of time from date of first dose of study drug to CV mortality and the associated 95% confidence intervals using Brookmeyer-Crowley methodology will be presented for each treatment group.

In addition, a stratified Cox proportional hazard model will be used to analyze time to CV mortality, with treatment group as the model covariate. The hazard ratio and associated 95% confidence intervals of the hazard ratio will be presented.

7.6.2.5 CV Hospitalization

The primary analysis for time from date of first dose of study drug to CV hospitalizations will be based upon a stratified Cox proportional hazard model using Anderson-Gill method to model recurrent events. To account for the correlation of CV events within each subject the Cox proportional hazards model will specify robust sandwich estimate for the covariance matrix. The hazard ratio and associated 95% confidence interval of the hazard ratio will be presented. In addition, we will calculate the cumulative hazard function every 6 months using Nelson-Aalen estimator.

7.6.2.6 All-cause Mortality

The primary analysis for time from date of first dose of study drug to all-cause mortality event will be based upon a stratified log-rank test to compare treatment groups. Definition details for All-cause Mortality are located in Appendix I.

The distribution of time from date of first dose of study drug to all-cause mortality for each treatment group will be generated using Kaplan-Meier (KM) plot. For each percentile (25^{th}, 50^{th}, 75^{th}) if reached, an estimate of time from date of first dose of study drug to CV mortality and the associated 95% confidence intervals using Brookmeyer-Crowley methodology will be presented for each treatment group.

In addition, a stratified Cox proportional hazard model will be used to analyze time to all-cause mortality, with treatment group as the model covariate. The hazard ratio and associated 95% confidence intervals of the hazard ratio will be presented.

The cumulative number of patients with an all-cause mortality event and associated percentage for each treatment group will be displayed. In addition, the total number of patients (and associated percentage) in each type of mortality event (CV, HF, not CV nor HF) will be displayed by treatment group.

7.6.3 Exploratory Efficacy Analysis

7.6.3.1 Echocardiogram (ECHO) Parameters

Descriptive statistics of actual value, change from baseline and percent change from baseline for selected ECHO parameters will be generated for each treatment group by visit.

Selected ECHO parameters are located in Appendix V.

7.6.3.2 Karnofsky Performance Status

Karnofsky Performance Status [KPS] will be categorized into 3 main categories (1=Able to carry on normal activity and to work, no special care [KPS range: 80-100], 2=Unable to work; able to live at home and care for most personal needs; varying amount of assistance [KPS range: 50-70], 3=Unable to care for self; requires hospital care; disease may be progressing rapidly [KPS range: 0-40]).

Descriptive statistics displaying a shift table of baseline KPS class category [range: 1-3] to each post-baseline visit categories [range: 1-3] will be generated. An overall shift of the baseline to worst post-baseline KPS class category will be presented for each treatment group

A frequency of each KPS category [0-100] will be generated for each treatment group at each visit.

7.6.3.3 Troponin T and I, and NT proBNP Levels

Descriptive statistics of actual value, change from baseline and percent change from baseline for each cardiac biomarker will be generated for each treatment group by visit.

7.6.3.4 Cardiac Magnetic Resonance (CMR) Imaging Parameters

Descriptive statistics of actual value, change from baseline and percent change from baseline for selected CMR parameters will be generated for each treatment group by visit.

Note: This procedure is only conducted at selected sites and only allowed to be performed on patients without contraindications (ie, pacemarkers, severe renal failure with eGFR, defibrillators or allergy to gadolinium). A summary of the sites that were selected to perform the test will be tabulated.

Selected CMR parameters are located in Appendix VI.

7.6.3.5 Technetium-99m Scintigraphy Parameters

Descriptive statistics of actual value and change from baseline for selecteechnetium-99m Scintigraphy parameters will be generated for each treatment group by visit.

Note: This procedure is only at selected sites. A summary of the sites that had the capabilities to perform the test will be tabulated.

7.6.3.6 Amyloid in Abdominal Wall Fat Pad Aspirates

Tabulations of result of test and grade of test will be generated for each treatment group by visit.

Note: This procedure is voluntary for the patients. A summary of sites where patients volunteered for this procedure will be tabulated.

7.6.3.7 Polyneuropathy Disability Score

PND score will be categorized into 4 categories:

Category 1: Stage 0=No symptoms

Category 2: Stage I=Sensory disturbances but preserved walking capabilities or

Stage II=Impaired walking capacity but ability to walk without a stick or cane,

Category 3: Stage IIIA=Walking with the help of one stick or crutch or

Stage IIIB=Walking with the help of two sticks or crutches

Category 4: Stage IV=Confined to a wheelchair or bedridden.

Descriptive statistics of a shift from baseline PND category [range: categories 1 -4] to post-baseline PND category [range: categories 1-4] at each follow-up visit will be presented by treatment group.

Additionally, the number of patients and associated percentage of each PND score stage at each visit will be presented by treatment groups.

7.6.3.8 Modified Body Mass Index

Modified body mass index is defined as Body Mass Index (BMI) multiplied by albumin level collected at the same visit.

Descriptive statistics of actual value, change from baseline and percent change from baseline for modified BMI will be generated for each treatment group by visit.

7.6.3.9 Estimated Glomerular Filtration Rate (eGFR)

Descriptive statistics of actual value, change from baseline and percent change from baseline for eGFR (mL/min/1.73 m^2) will be generated for each treatment group by visit. Additionally, categorical shifts in eGFR [(≥15-30), (≥30-60), (≥60-90), ≥90)] from baseline to worst post-baseline eGFR category will be generated for each treatment group.

7.6.3.10 Heart Failure (HF) Hospitalization

The time from date of first dose of study drug to HF hospitalization will be a stratified Cox proportional hazard model using Anderson-Gill method to model recurrent events. To account for the correlation of CV events within each subject the Cox proportional hazards model will specify a robust sandwich estimate for the covariance matrix. The hazard ratio and associated 95% confidence interval of the hazard ratio will be presented.

The cumulative number of HF hospitalizations per patient reported during each visit intervals [>0 to ≤ 6 months, >6 to ≤ 12 months or >12 to ≤ 18 months and >0 to ≤18 months] will be presented for each treatment group. Additionally, at each visit interval, the cumulative number of HF hospitalizations and percentage of patients with a HF hospitalization event will be tabulated.

7.6.3.11 EQ-5D-5L

Descriptive statistics of Index score (US reference), and VAS at baseline will be presented by treatment groups at each visit. For each of the 5 dimensions (Mobility, Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression), a frequency (and associated percentage) of the number of patients who reported the levels of symptom will be presented by treatment group at each visit. Change from baseline in each of the summary scores (Index score and VAS) will be presented for each treatment group. For each of the 5 dimensions, a shift table of baseline to worst post-baseline shift of symptoms of the EQ-5D questionnaire will be presented by treatment group.

Additional details of the EQ-5D-5L questionnaire are located in Appendix V.

7.6.3.12 Pharmacoeconomic Questionnaire (PEQ)

Frequency (percentage) of the following parameters will be summarized by treatment group and visits:

- Number (No.) of Visits to General Practitioner
- No. of Visits to Specialist Physician in less 6 months
- No. of Visits to the ER in the last 6 months due to FAC
- Level of Function categories (eg, able to work full time and live at home, unable to work)
- Symptoms experienced in the last month
- Caregiver ability to retain a job

A per patient listing will also be generated of the responses to the PEQ questionnaire.

7.7 Safety

All safety analyses will be analyzed using the Safety Population. The safety analysis will be summarized by the treatment that was actually received. If a patient received at least one dose of revusiran, he/she would be grouped in the revusiran arm for safety analyses.

7.7.1 Adverse Events

All safety analyses will be based on treatment emergent adverse events (AEs) and will be summarized by treatment received. A treatment-emergent AE is defined as any AE occurring or worsening in severity after the first dose (including date/time) of study drug administration through 28 days after the last dose, or any event that was present at baseline but worsened in intensity or was subsequently considered drug-related by the Investigator. AEs will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA Version 17.1 or later) by System Organ Class (SOC) and Preferred Term (PT). All treatment emergent AEs hereafter will be referred to as AEs in this document.

An overview of the frequency (percentage) of AEs will be tabulated (such as but not limited to, the number of patients with at least 1 AE, the number of patients with at least 1 AE related to study drug, the number of patients with a severe AE, the number of patients with at least 1 SAE, and the number of patients who discontinued study drug due to an AE). Separate tabulations will be produced for all AEs, AEs by maximum severity, treatment-related AEs by severity, serious adverse events (SAEs), discontinuation from study drug due to AEs and deaths. These tabulations will be presented by SOC and PT. In addition, a summary table of all AEs and SAEs sorted by decreasing frequency based on PT for each treatment group will be generated. Any AEs leading to discontinuation of study drug, death and any SAEs will be presented in patient listings.

Additional summary tables of AEs by SOC and PT per treatment group include the following:

- Frequent SAEs [defined as SAEs occurring in ≥5% in either treatment group]
- Frequent AEs [defined as AEs occurring in ≥ 10% in either treatment group]
- CV Hospitalizations*
- CV Mortality*
- HF Hospitalizations*

*Note: The classification of death and hospitalization events will be determined by an independent Clinical Adjudication Committee (CAC).

Event of Special Interest: Injection Site Reactions [ISRs]. ISRs are defined as any AEs which maps to the HLT='Injection Site Reactions' using MedDRA dictionary.

The following summary will be generated by treatment group:

- Frequency (percentages) of ISRs by HLT and PT
- Frequency (percentage) of ISRs by maximum severity, HLT and PT
- Listing of study drug discontinuation due to an ISR

No formal hypothesis-testing analysis of AE incidence rates will be performed.

7.7.2 Laboratory Evaluations

Clinical laboratory events will be expressed in SI units. Out-of-reference-range values will be flagged as high (H) or low (L) in the listings. For analysis purposes, values preceded by a "<" or a ">"sign (i.e. those below or above the limits of quantification) will be considered equal to the lower or upper limit of quantification, respectively. Appendix VIII contains the laboratory parameters.

Summary data for each laboratory parameter will be presented for each continuous clinical laboratory parameter (including hematology, serum chemistry, coagulation, liver function test, and thyroid test). Descriptive statistics will be generated for actual values, change from baseline, and percent change from baseline.

A shift table of laboratory parameters of the baseline category to the worst post-baseline category will be based upon the upper or lower limits of the normal range. All out-of-range outside the normal ranges will be presented in patient listings.

Event of Special Interest: Liver Function Evaluations (LFTs)

The following summaries will be generated for LFTs:

- Boxplots displaying the distribution of the ratio of result/ULN at each scheduled visit by treatment group.
- Plots of concurrent and non-concurrent peak bilirubin versus peak ALT or AST will be presented by treatment group.
- 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 by treatment group. Categories for shift table are ≤ ULN, >ULN to < 3 x ULN, ≥ 3×ULN to ≤ 5 x ULN, > 5 x ULN to ≤ 10 x ULN, > 10 x ULN to ≤ 20 x ULN
- Frequency (percentage) of patients with elevations of LFTs across various ULN categories:
  - ALT > 3xULN, >5xULN, >10xULN, >20xULN
  - AST >3xULN, >5xULN, >10xULN, >20xULN
  - ALT or AST >3xULN, >5xULN, >10xULN, >20xULN
  - Total bilirubin >2xULN
  - ALT or AST >3xULN and total bilirubin >2xULN
  - ALT or AST >3xULN, total bilirubin >1.5xULN, and ALP <2xULN
  - ALT or AST >3xULN, total bilirubin >2xULN, and ALP <2xULN

In addition, a separate listing of LFT values outside the normal range will be listed separately.

7.7.3 Ophthalmologic Examination

An ophthalmic exam will be conducted in addition to a slit lamp examination. For each eye and eye structure (iris, conjunctiva, anterior chamber, cornea, 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 treatment group and visit.

A per patient listing of the results of the ophthalmic exam at any visits with an overall assessment of abnormal, clinically significant result will be generated.

7.7.4 Vital Signs, Body Weight and BMI

Descriptive statistics will be provided for all vital signs including blood pressure (Systolic (mmHg), Diastolic (mmHg), pulse rate (bpm), oral body temperature, respiration rate (breaths/min), weight (kg), and BMI (kg/m^2).

Change from baseline in vital signs will be summarized by visit and treatment group using descriptive statistics.

An outlier analysis of vital signs will be performed to summarize the frequency (associated percentage) of abnormal values at post-baseline visits (scheduled or unscheduled) by treatment groups for the following parameters (Temperature, Pulse, Systolic Blood Pressure, Diastolic Blood Pressure).

7.7.5 Electrocardiograms

ECG parameters, including ventricular rate, PR interval, QRS duration, max QRS amplitude, QT interval will be collected at each visit. ECG parameters for Bazett corrected QT (QTcB) interval [calculated: QT x $(\text{Heart Rate}/60)^{1/3}$ msec] and Fridericia corrected QT (QTcF) interval [calculated; QT x $(\text{Heart Rate}/60)^{1/2}$msec] will be derived for each visit. Overall categorical assessments including rhythm, electrical pacing present in ECG, ST or T-wave changes, A-V Block, Ventricular Conduction defect, Infarct pattern/poor r-wave progression and overall ECG interpretation is collected at each visit.

Descriptive statistics will be used to summarize continuous parameters by visit and treatment group.

Frequency (associated percentage) of each of the overall categorical assessments will be summarized as well by visit and treatment group. A separate per patient listing will be generated displaying all ECG values for any patient with an overall interpretation on ECG classified as Abnormal, Clinically Significant.

An outlier analysis will be performed to summarize the frequency (associated percentage) of abnormal values at post-baseline visits (scheduled or unscheduled) by treatment groups for the following parameters (QTc, QTcB, QTcF, PR, QRS and HR).

The ECG measurements and changes from baseline as well as investigator assessment and interpretation will be provided in a data listing.

7.7.6 Physical Examination

For each body system, the frequency (and associated percentage) of patients with a categorical result of (Normal, Abnormal – Not Clinically Significant, Abnormal – Clinically Significant) will be presented by treatment group and visit.

Physical examination results will be provided in a data listing. Abnormal, Clinically Significant findings will be presented in a separate listing.

7.7.7 Anti-Drug Antibodies (ADA)

A tabular summary of the ADA results at each visit will be generated. A patient listing of any subjects with a positive result will be generated.

7.7.8 Exploratory Biomarkers

Exploratory biomarkers collected will be presented in a patient listing.

7.8 Interim Analysis

An unblinded interim analysis for futility may be conducted by the unblinded DMC statistician once approximately half the patients have completed the study. The Statistical Analysis Plan will be updated to address the futility criteria.

8 REFERENCES

1. Finkelstein, D.M., and Schoenfeld, D.A. Combining mortality and longitudinal measures in clinical trials. Stat Med 1999; 18, 1341-1354.

9 APPENDICES

Appendix I Details for Co-primary and Secondary Endpoints

A stratified Finkelstein and Schoenfeld Joint Rank Test will be used for the co-primary efficacy endpoint of change from baseline in 6-MWD at 18 months. Pairwise comparison of patients to determine their ranking will be performed using the following steps:

Step 1: Comparison based on time to death

Definition of time to death: Time from date of first dose of study drug to death (months) will be calculated as: (date of death – date of date of first dose of study drug + 1)/30.4. If a patient did not die, time from date of first dose of study drug to death (censoring time) will be calculated as: (date of last study visit –date of first dose of study drug+1)/30.4. Time from date of first dose to death will allow values up to Month 18 analysis visit.

Comparisons can be made if:

- Both patients died and there is no tie in the survival time
- One patient died and the other patient did not die and the time of the death for the patient that died was $\leq$ the time to death for the patient that did not die (censoring time).

Comparison will be inconclusive if:

- Both patients died and the time to death is a tie
- Both patients were alive
- One patient died and the other patient did not die, and the time of death for the patient was $>$ the time to death of the patient that did not die (censoring time).

Step 2: Comparison based on time to loss of ability to perform 6-MWD

Definition of time to loss of ability to perform 6-MWD:

Loss of ability will be indicated if any of these scenarios occur:

- A patient could not perform the test without an additional walking aids compared to the walking aid used at the screening visits
- A patient could not perform the test without an increase in oxygen flow compared to the oxygen flow used at the screening visits.
- If at a scheduled study visit the patient was unable to perform the test due contraindications (such as: unstable angina within the last month, myocardial infarction within the last month, resting heart rate>120 beats a minute, systolic blood pressure>180 mmHg, diastolic blood pressure>100 mmHg, hospitalization within 2 weeks or other reasons specified (eg, wheelchair)).

The time of loss of ability to perform 6-MWD will be based upon the analysis visit. A patient may have more than one onset time for loss of ability to perform 6-MWD during the study. For a patient with more than one scheduled visit where the patient was unable to perform the test, the time of loss will be at the visit where the patient lost and never regained the ability to walk. For a patient not considered to have lost the ability to walk, the time from loss of ability (censoring time) will be calculated as: (date of the latest 6MWD – date of first dose +1)/30.4. Time from first dose to loss of ability will allow values up to Month 18 analysis visit. Note: Any patient that is able to perform the walk at Month 18 visit will be considered a censored patient.

Comparison can be made if:

- Both patients indicated a loss of ability and there is no tie in the time to loss (scheduled visit)
- One patient indicated a loss of ability and the other did not, and the time of the patient who lost the ability to perform the test was ≤ the time of the patient who did not lose the ability to perform the test (censoring time).

Comparison will be inconclusive if:

- Both patients indicated a loss of ability and there is a tie in the time to loss (scheduled visit)
- Both patients did not indicate a loss of ability
- One patient indicated a loss of ability and the other patient did not, and the time of the patient who lost the ability to walk > the time of the patient who did not lose the ability to walk (censoring time).

Step 3: Comparison based on change from baseline in 6-MWD

Definition of change from baseline in 6-MWD: Change in 6-MWD (meters) from baseline will be calculated as: (distance walked at post-baseline visits – distance walked at baseline). Baseline will be defined as stated in section 6.1.

To compare change from baseline in 6-MWD (meters) for a pair of patients, the latest common post-baseline study visit that both patients had 6-MWD measurements will be compared. In the event that the change in distance walked from baseline between the pair of patients is identical, a score of 0 (inconclusive) will be assigned to both patients.

Additional details:

- If a patient had > 0 meters for 6-MWD at month 18 and the patient died within month 18 analysis window, then the patient will be considered unable to perform 6-MWD at month 18.
- If a patient did not have any post-baseline information (eg, no information on survival status and no post-baseline data regarding 6-MWD), then the patient will be inconclusive for all comparisons.

Prior to the database lock, data collected from the 6-MWD test will be carefully reviewed to identify unexpected scenarios.

Secondary endpoint: Composite CV Mortality and CV Hospitalization

Step 1: Comparison based on time to CV mortality

Definition of time to CV mortality: Time from date of first dose of study drug to CV death (months) will be calculated as: (date of death due to CV – date of first dose of study drug + 1)/30.4. If a patient did not die due to CV, time from first dose of study drug to CV death (censoring time) will be calculated as: (date of last study visit/date of death not due to CV – date of first dose of study drug+1)/30.4. Time from first dose of study drug to CV mortality will allow values up to Month 18 analysis visit.

Comparisons can be made if:

- Both patients died due to CV and there is no tie in the survival time
- One patient died due to CV and the other patient did not die due to CV and the time of the CV mortality ≤ the time to CV mortality for the patient that did not die (censoring time).

Comparison will be inconclusive if:

- Both patients died due to CV and the time to mortality is a tie
- Both patients died (not due to CV)
- Both patients were alive
- One patient died (not due to CV mortality) and one patient was alive
- One patient died due to CV and the other patient did not die due to CV, and the time of CV mortality was > the time to CV mortality of the patient that did not die (censoring time).

Step 2: Comparison based on number of CV hospitalizations

Definition of number of CV hospitalizations: For each patient, the cumulative number of CV hospitalizations will be tabulated starting from the date of the first dose of study drug until up to Month 18 analysis visit.

To compare the number of CV hospitalizations for a pair of patients, the total number of CV hospitalizations up to the latest common time on study will be compared. In the event that the total number of CV hospitalizations is identical between the pair of patients, a score of 0 (inconclusive) will be assigned to both patients.

Secondary endpoint: Change in NYHA from Baseline

Step 1: Comparison based on time to death

This comparison will use the same assumptions as stated for the co-primary endpoint.

Step 2: Comparison change in NYHA class from baseline

Definition of change in NYHA class from baseline: Change in NYHA class from baseline is defined as: (NYHA class at post-baseline visit – baseline NYHA class). Baseline will be defined as the latest NYHA measurement prior to study drug. The possible range of values for change in NYHA is +3 (deterioration in health status) to -3 (improvement in health status). A positive change would indicate deterioration in health from baseline and a negative change would indicate an improvement in health from baseline.

The possible values of NYHA class at a visit are as follows:

- Class I coded as 1
- Class II coded as 2
- Class III coded as 3
- Class IV coded as 4

To compare the change in NYHA class from baseline for a pair of patients, the latest common post-baseline study visit that both patients had a non-missing NYHA result will be compared. In the event the change in NYHA from baseline between a pair of patients is identical, a score of 0 (inconclusive) will be assigned to both patients.

Additional details:

- If a patient did not have any post-baseline information (eg, no information on survival status and no post-baseline data regarding NYHA), then the patient will be inconclusive for all comparisons.

Secondary endpoint: Change in overall summary score (KCCQ) from Baseline

Step 1: Comparison based on time to death
This comparison will use the same assumptions as stated for the co-primary endpoint.

Step 2: Comparison change in overall summary score from baseline

Definition of change in overall summary score from baseline: Change in overall summary score from baseline is defined as: (overall summary score at post-baseline visit – baseline overall summary score). Baseline will be defined as the latest overall summary score measurement prior to study drug. The possible range in change in overall summary score is -100 (deterioration in health status) to +100 (improvement in health status). A negative change would indicate deterioration in health from baseline and a positive change would indicate an improvement in health from baseline.

To compare the change in overall summary score from baseline for a pair of patients, the latest common post-baseline study visit that both patients had a non-missing overall summary result will be compared. In the event the change in overall summary score from baseline between a pair of patients is identical, a score of 0 (inconclusive) will be assigned to both patients.

Additional details:

- If a patient did not have any post-baseline information (eg, no information on survival status and no post-baseline data regarding overall summary score), then the patient will be inconclusive for all comparisons.
- If a patient had a missing baseline overall summary score and did not die, then the patient will be inconclusive for all comparisons.

Secondary endpoint: CV Mortality

Definition of time to CV mortality: Time from first dose of study drug to CV death (months) will be calculated as: (date of death due to CV – date of first dose of study drug + 1)/30.4. If a patient did not die due to CV, then time from first dose of study drug to CV death (censoring time) will be calculated as: (date of last study visit/date of death not due to CV – date of first dose of study drug+1)/30.4. Time from first dose of study drug to CV mortality will allow values up to Month 18 analysis visit.

Secondary endpoint: All-cause Mortality

Definition of time to all-cause mortality: Time from first dose of study drug to all-cause death (months) will be calculated as: (date of death (any reason for death) – date of first dose of study drug + 1)/30.4. If a patient did not die, then time from first dose of study drug to all-cause mortality (censoring time) will be calculated as: (date of last study visit – date of first dose of study drug+1)/30.4. Time from first dose of study drug to all-cause mortality will allow values up to Month 18 analysis visit.

Appendix II Computational Procedure of Finkelstein and Schoenfeld Joint Rank Test

[redacted]

Table A3-1 Sample Data for 6 Patients

[redacted]

Table A3-2 Finkelstein and Schoenfeld Joint Rank Test on the Sample Data

[redacted]

[redacted]

Appendix III Kansas City Cardiomyopathy Questionnaire (KCCQ) Measure and Scoring

The Kansas City Cardiomyopathy Questionnaire is a 23-item, self-administered instrument that quantifies aspects of the health-related quality of life of patients. Specifically, this instrument yields several clinically relevant domains: physical limitations, severity, symptom stability, self-efficacy, social interference, and quality of life. In also yields two summary scores: functional status and clinical summary scores. An example of a questionnaire item is "Over the past 2 weeks, how many times did you have swelling in your feet, ankles or legs when you woke up in the morning?" with responses ranging from 1 (every morning) to 5 (never in the past 2 weeks).

The KCCQ consists of the following clinically relevant domains:

- Physical Limitations (question 1)
- Symptoms
  - Symptom Frequency [redacted]
  - Symptom Burden [redacted]
  - Symptom Stability (i.e., change over time, question 2)
- Total Symptom Score = mean of Symptom Frequency and Symptom Burden scores
- Self-Efficacy [redacted]
- Social Limitations [redacted]
- Quality of Life [redacted]
  - [redacted]

To facilitate interpretability, two summary scores were developed.

- KCCQ Clinical Summary Score (KCCQ-cs): Combining the Physical Limitation and Total Symptom Score.
- KCCQ Overall Summary Score (KCCQ-os): An overall score is calculated by taking the mean of the Physical Limitation and Total Symptom Score with the Quality of Life Score and Social Limitation Scores.

The KCCQ scales are scored by assigning an ordinal value to each response, beginning with 1 for the response that implies the lowest level of functioning and summing items within each domain. Missing values within each KCCQ domain are imputed according to the scoring algorithm (see below) supplied by the instrument developer (Dr. Spectus). Items are then summed to generate a total score and transformed to a scale with a range of 0 to 100, such that high scores indicate greater levels of functioning.

The Kansas City Cardiomyopathy Questionnaire Scoring Instructions

There are 10 summary scores within the KCCQ, which are calculated as follows:

1. Physical Limitation

[redacted]

[redacted]

2. Symptom Stability

[redacted]

3. Symptom Frequency

[redacted]

[redacted]

4. Symptom Burden

[redacted]

5. Total Symptom Score = mean of the following available summary scores:

[redacted]

6. Self-Efficacy

[redacted]

7. Quality of Life

[redacted]

8. Social Limitation

[redacted]

9. Overall Summary Score = mean of the following available summary scores:

[redacted]

10. Clinical Summary Score = mean of the following available summary scores:

[redacted]

[redacted]

Appendix IV EQ-5D-5L Measure and Scoring

The EQ-5D-5L consists of 2 parts: the EQ-5D-5L descriptive system and the EQ visual analog scale (VAS). The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension has 5 levels of severity: no problems (1), slight problems (2), moderate problems (3), severe problems (4), and extreme problems (5). The EQ VAS records the patient's self-rated health on a 20-cm vertical VAS with endpoints labeled "The best health you can imagine" and "The worst health you can imagine." This information can be used as a quantitative measure of health as judged by the individual respondents.

Based on the patient's response to each of the 5 dimensions, a 1-digit number expressing the level selected for that dimension will be recorded. The digits for the 5 dimensions will then be combined in a 5-digit number describing the respondent's health state. Each of the 5-digit combinations refers to a country-specific index value defining the health state of the patient.

As index-based values have not been evaluated for the EQ-5D-5L at this time, crosswalk value sets developed based on the EQ-5D-3L index-based values will be applied. The crosswalk value set for the US will be used for all countries. The value set provides an index score for each health state and can be accessed at: (http://www.euroqol.org/fileadmin/user_upload/Documenten/Excel/Crosswalk_5L/EQ-5D-5L_Crosswalk_Value_Sets.xls).

Appendix V Selected ECHO Parameters

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 VI Selected CMR Parameters

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	
Stroke Volume	

Appendix VII Laboratory Parameters

Hematology	Serum Chemistry	Urinalysis
Hematocrit Hemoglobin Red blood cell (RBC) count White blood cell (WBC) count Mean corpuscular volume Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Neutrophils, absolute and % Lymphocytes, absolute and % Monocytes, absolute and % Eosinophils, absolute and % Basophils, absolute and % Platelet count	Sodium Blood urea nitrogen (BUN) Creatinine Uric acid Lactate dehydrogenase (LDH) Glucose Potassium Phosphate Albumin Calcium Carbon dioxide Chloride	Visual inspection for appearance and color pH (dipstick) Specific gravity Ketones Protein Glucose Bilirubin Nitrite RBCs Urobilinogen Leukocytes Microscopy (if clinically indicated)
Liver Function Tests	**Coagulation Studies**	**Thyroid Function Test**
ALT AST Alkaline phosphatase (ALP) Bilirubin (total and direct)	Prothrombin time (PT) Activated partial thromboplastin time (aPTT) International Normalized Ratio (INR)	Thyroid stimulating hormone (TSH)
Pregnancy Testing	**Serology Parameters**	**Other**
β-human chorionic gonadotropin	Hepatitis B surface antigens (HBsAg) Anti-hepatitis C virus antibodies (HCV Ab) Hepatitis B surface antibodies (HBsAb)	Vitamin A B-type natriuretic peptide Serum SPEP with IFE Urine SPEP with IFE Serum FLC