Protocol B3461028

A MULTICENTER, INTERNATIONAL, PHASE 3, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED STUDY TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF DAILY ORAL DOSING OF TAFAMIDIS MEGLUMINE (PF-06291826) 20 MG OR 80 MG IN COMPARISON TO PLACEBO IN SUBJECTS DIAGNOSED WITH TRANSTHYRETIN CARDIOMYOPATHY (TTR-CM)

Statistical Analysis Plan (SAP)

Version: 5

Author: PPD

PPD

Date: 30-Jan-2018

Table 1. Revision History

Version	Date	Author(s)	Summary of Changes/Comments
Version 1.0	October 8, 2013	PPD	Original SAP
Version 2.0	May 19 , 2014	PPD	Amended to reflect the protocol amendment 1 and agreements with regulatory authorities.
Version 3.0	March 26, 2015	PPD	Amended to reflect the protocol amendment 2 and removed specification of a table.
Version 4.0	June 15, 2016	PPD	Amended to reflect the protocol amendment 3
Version 5.0	Jan 30, 2017	PPD PPD	Amendment to make minor corrections to the SAP

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APPENDICES

1. AMENDMENTS FROM PREVIOUS VERSION(S)

- **Status of study when amendment made:**

  Study is ongoing and remains blinded.

- **Details of Changes and Rationale:**

Amendment 1 (SAP Version 2)

Section of the SAP	Summary of change	Rationale
Various sections	Typographical corrections and clarifications For example: Changed "patients" to "subjects" for consistency.	Corrected minor typographical errors and inconsistent terminology.
2.1 Study Design	• Clarified specification of sample size as 400 subjects. • Specified the duration of 30 months to be equal to 910 days.	Inserted new text from protocol amendment 1.
5.6.2. Deviations Assessed Post Randomization	Added use of 3 prohibited medications, ie, diflunisal, tauroursodeoxycholate, and doxycycline as criteria for exclusion from Per-Protocol Analysis Set.	Use of prohibited medication as described in protocol amendment 1 Section 5.8.1. Contraindicated Therapies.
6.1.4. Exploratory Endpoints	Added echo strain and other parameters.	Inserted new text from protocol amendment 1.
8.1.1. Finkelstein Schoenfeld Analyses	• Clarified text around algorithm involving "censored" subjects. • Removed sentence related to analysis of "indeterminate" events.	• Modified text to improve clarity. • Removed sentence regarding analysis of events adjudicated as "indeterminate" as it was inconsistent with the last sentence of the first paragraph of Section 8.1.1.
8.2.2. Key Secondary Analyses	Added specification of pattern mixture analysis as a supplemental analysis of the key-secondary analyses.	Inserted new text per agreement with FDA.
8.2.3. Secondary Analyses	Added a statement describing the handling of deaths adjudicated as "indeterminate" similar to the handling of "hospitalizations".	Added missing detail for handing "indeterminate" deaths in the analysis.
8.2.4. Exploratory Analyses	• Added analysis of placebo vs 80 mg randomized subjects who were not downtitrated as requested by PMDA. • Added analysis by region as requested by FDA. • Added additional exploratory endpoints.	• Added analysis requested by PMDA and FDA. • Added exploratory endpoints to be consistent with protocol amendment 1.

Table 2 Summary of Proposed Efficacy and Safety Analyses	Updated to reflect the changes to SAP.	Table updated to be consistent with the body of SAP and protocol amendment 1.
Appendix 1.2. Sample SAS Code for Analyses	• Added code for pattern-mixture. • Made a minor correction to the SAS code for analyses described in Section 8.1.3, ie, added RANDOM statement.	• Added SAS code for new pattern-mixture analysis consistent with May 2014 agreement with FDA. • Made minor correction to previous SAS code.

Amendment 2 (SAP Version 3)

Section of the SAP	Summary of change	Rationale
Sections 2.1, 8.1.1, 8.1.2, 8.2.4	Cardiac mechanical assist device was added as a reason for discontinuation and treated similar to heart transplant in the analysis.	Cardiac mechanical assist device is indicative of end stage disease similar to a heart transplant.
Section 8.2.5	Removed specification of an unnecessary table.	Listing of adverse events occurring during the trial will include those that start prior to randomization.

Amendment 3 (SAP Version 4)

Section of the SAP	Summary of change	Rationale
Sections 6.4, 8.1.1, 8.1.2, 8.1.3, 8.1.4, 8.1.5, 8.1.6, 8.2.4	NYHA baseline classification categories were change from "NYHA class I and NYHA classes II and III combined " to "NYHA classes I and II combined and NYHA class III".	Redefined the baseline groupings for New York Heart Association (NYHA) Functional Classification that will be used for efficacy analyses, grouping subjects with NYHA Class I and II together to be compared against NYHA Class III. Given the very low number of enrolled subjects with NYHA Class I, the NYHA baseline groupings were redefined for efficacy analyses. This permits a more appropriate baseline adjustment in the primary analysis as well as other secondary and exploratory analyses.
Section 2.1	Study number of the extension study included and other edits.	Edits to reflect the changes to the protocol.
Section 6.1.4, Section 8.2.4, Table 2	KCCQ subjects symptoms subscales clarified.	Better delineated the analysis planned for Kansas City Cardiomyopathy Questionnaire (KCCQ) scores related to subject symptoms.
Section 6.2	Text updated to be consistent with protocol.	The italicized text was update to be consistent with protocol.

[redacted]

Section 8.1.1, Section 6.4	Clarification of how subjects incorrectly classified during randomization will be handled in the primary analysis.	Subjects who were incorrectly classified during randomization will be analyzed using the correct value of the stratification factors (TTR Genotype or NYHA baseline classification) in the primary analysis.
Section 8.2	Frequency of TTR mutation analysis added.	Frequency of various TTR mutations enrolled in the study will be summarized.
Section 8.2.1, Section 8.2.4	Clarified the term "down-titration" to "dose reduction".	Wording modified per protocol to more accurately represent the change in dose that may occur when a subject is unable to tolerate the randomized dose.
Section 8.2.4	Cross-tabulation summary added for Patient Global Assessment.	Additional descriptive summary for Patient Global Assessment added.
Section 8.2.5	A lag of 28 days will be used in determining treatment-emergence.	Clarifying and documenting a program wide standard procedure with respect to lag.
Appendix 1.2	Visit window algorithm details added.	An algorithm was added to detail how early termination visits will be assigned to nominal study visits.

Amendment 4 (SAP Version 5)

Section of the SAP	Summary of change	Rationale
6.1.4. Exploratory Endpoints	Updated KCCQ related domain and summary scores.	Updated to be consistent with the developers' names for the KCCQ domain and summary scores.
8.1.1. Finkelstein Schoenfeld Analyses	Corrected an error in the notation (replace subscript "i" with "j") describing the calculation of Ui.	Update to correct a minor error in the equation describing calculation of Ui ($U_i = \sum_{j \in A_k} u_{ij}$)
8.2.2. Key Secondary Analyses	Updated reference for sample SAS code for pattern mixture analysis from Appendix 1.2 to Appendix 1.3.	Updated to correct the referenced Appendix number.
8.2.4. Exploratory Analyses	Removed exploratory analysis comparing subjects reduced to 40 mg vs placebo.	The analysis is not meaningful given the very low number of total blinded dose reductions in the study.
8.2.4. Exploratory Analyses	Added tables summarizing plasma concentrations of tafamidis and a listing of plasma concentration of diflunisal.	Added plasma based summary tables for tafamidis and listing for diflunisal.
8.2.5. Safety Analyses	Added by-gender summary tables for treatment-emergent adverse events and serious adverse events.	Added analyses evaluating gender based differences in adverse events between the study treatments.
Table 2	Updated KCCQ related domain and summary scores.	Updated to be consistent with the developers version of KCCQ.
Appendix 1.2	Updated windowing for Echocardiogram endpoints.	Added details of the windowing algorithm for Echocardiogram endpoints based on the study visits when they were collected.

Appendix 1.3	Updated sample SAS code for pattern mixture code.	Update code to fix an error in the ESTIMATE statement in the sample SAS code.
Appendix 1.3	Updated sample SAS code to use PROC GLM replacing PROC ANOVA.	Replaced PROC ANOVA with, PROC GLM which is a more appropriate procedure for un-balanced data.
Appendix 1.4. Details of Multiple Imputation Method to be Used in Sensitivity Analysis	Details to text and SAS code added.	Added details to text and SAS code to improve clarity.

2. INTRODUCTION

Amyloidosis is a severely debilitating condition induced by the accumulation of various insoluble fibrillar proteins, or amyloid, within the tissues in amounts sufficient to impair normal function. Different precursor proteins have been associated with amyloid cardiomyopathy, including immunoglobulin light chains (associated with primary or AL amyloidosis), serum amyloid A (associated with secondary or AA amyloidosis) and transthyretin (TTR) representing the most common inherited amyloidosis. Transthyretin (also referred to as pre-albumin), a 127-amino acid, 55 kDa protein that is primarily synthesized in the liver, is a transport protein of thyroxine and retinol-binding protein-retinol (vitamin A) complex (Blake 1978, Monaco 1995). A mutation in TTR accelerates the process of fibrillogenesis whereby the tetrameric structure of the TTR protein dissociates leading to amyloid deposition (Nilsson 1975, Saraiva 2001). Dissociation of the TTR tetramer into monomers is the initial and rate-limiting step in amyloidogenesis (Nilsson 1975, Saraiva 2001).

Transthyretin amyloidosis can present as either a hereditary or an age-related disease. The major phenotypic presentations of TTR amyloidosis include transthyretin familial amyloid polyneuropathy (TTR-FAP), which can present with sensorimotor and autonomic polyneuropathy and transthyretin cardiomyopathy (TTR-CM), which can present in either a genetic variant or a wild-type form (the latter is also known as senile systemic amyloidosis or SSA).

Median survival from diagnosis for patients with TTR-CM was 41 months in a study of the V122I mutation and median survival was reported as 46 months for wild-type (Connors 2011). Death in most patients with cardiac amyloidosis is from cardiac causes, including sudden death, heart failure, and myocardial infarction (Kyle 1996, Smith 1984).

Tafamidis is an oral small molecule, under development by Pfizer, as a disease modifying therapy for TTR amyloid diseases. It binds to the thyroxine binding sites on the TTR tetramer, thereby preventing destabilization into the monomeric form. In study Fx1B-201, tafamidis effectively stabilized TTR in 34 of 35 (97.1%) subjects, representing both wildtype and V122I, at Week 6, with approximately 88% stabilized throughout the 12 months of the study. Of note, tafamidis has also been studied in TTR-FAP and effectively stabilized TTR in 98% of subjects as well as demonstrating effects relative to placebo on clinical measures (Coelho 2012).

TTR-CM is a rare disease with very little available published information. Based on this, the natural history and disease progression of TTR-CM were prospectively evaluated in a noninterventional study involving 29 subjects (Transthyretin Amyloidosis Cardiac Study [TRACS]; Study Fx-001; Ruberg 2012). In addition, subsequent to the TRACS study, an open-label, Phase 2 Study Fx1B-201 was initiated. This study involved 35 subjects with TTR-CM who received open-label tafamidis 20 mg QD for 12 months along with routine standard of care. The proportion of patients with the variant genotype was substantially lower in Fx1B-201 compared with TRACS.

2.1. Study Design

This is a Phase 3, multicenter, international, three-arm, parallel design, placebo-controlled, randomized study with a 30-month double-blind treatment phase, to determine efficacy, safety and tolerability of tafamidis on clinical outcomes in subjects with either transthyretin genetic variants or wild-type transthyretin resulting in amyloid cardiomyopathy (TTR-CM).

There will be approximately 400 subjects enrolled in the study in a 2:1:2 ratio (placebo:20 mg:80 mg). The subjects will be allocated to the 3 arms of the study in the following manner: n=160 in the placebo arm, n=80 in the 20 mg arm, and n=160 in the 80 mg arm. Subjects who experience adverse events that may be associated with poor tolerability to treatment with tafamidis that may impact dosing adherence have the option of blinded treatment re-assignment and potential dose-reduction (see Section 5.5 of protocol). Subjects will be stratified during enrollment by TTR genotype (variant and wild-type) and structured such that greater than 30% of randomized subjects have a TTR mutation and greater than 30% of subjects have a diagnosis of wild-type TTR cardiomyopathy, with the intent to enroll comparable numbers between the variant and wild-type groups.

Enrollment may be closed for either wild-type or variant stratum in order to enroll at least 30% of subjects with each TTR genotype (wild-type and variant).

Additionally, stratification to treatment assignment will be done for Baseline severity of disease based on NYHA classification (NYHA Class I and NYHA Classes II and III combined). Stratification will be implemented in order to maintain a balance of both TTR genotype and disease severity across the treatment assignments. The site will ensure a Month 30 follow-up contact to determine the subject's vital status and whether the subject has had a heart and / or liver transplant or implantation of cardiac mechanical assist device. Upon completion of the study at the Month 30 visit, subjects may be eligible for treatment with tafamidis in a separate study (B3461045), which will permit the collection of additional safety and efficacy data, and may include the assessment of hospitalizations, mortality, and other outcomes relating to disease progression. For the purpose of this study, 30 months is defined as 910 days. Eligibility for the extension study (B3461045) requires subject participation in this study at least through Day 896 (Month 30 minus 2 weeks).

2.2. Study Objectives

The primary objective of this study is to assess the efficacy of an oral dose of 20 mg or 80 mg tafamidis meglumine soft-gel capsules based on all-cause mortality and on frequency of cardiovascular-related hospitalizations as well as to assess safety and tolerability in comparison to placebo. Tafamidis or placebo will be administered once daily, in addition to standard of care, for 30 months in subjects diagnosed with variant or wild-type TTR cardiomyopathy (TTR-CM).

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

No formal efficacy interim analysis is planned.

The E-DMC will be responsible for ongoing monitoring of the safety of subjects in the study according to the E-DMC Charter through safety interim analyses consisting of comparisons of safety information across treatment groups. Un-blinded descriptive summaries of mortality, hospitalization, adverse events, laboratory data, and other safety monitoring data as requested by the E-DMC will be provided for their review.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

The null hypothesis for the primary analysis is that neither all-cause mortality nor frequency of cardiovascular-related hospitalizations is different between the tafamidis and placebo treatment groups. The corresponding alternative hypothesis is that at least one and possibly both all-cause mortality and frequency of cardiovascular-related hospitalizations are different between the tafamidis and placebo treatment groups.

4.2. Statistical Decision Rules

All hypothesis testing will be conducted using two-sided tests with alpha = 0.05 level of significance. The list of key-secondary endpoints and the methodology for controlling the study-level Type I error at 0.05 due to multiple analyses are detailed in Section 8.2.2.

5. ANALYSIS SETS

The following sets are defined for use in the analyses:

- Intent-To-Treat (ITT) Analysis Set;
- Per-Protocol (PP) Analysis Set;
- Safety Analysis Set.

Both the ITT and PP analysis sets will be used for the primary analysis and for the analyses of the key-secondary endpoints, with the ITT being primary. The secondary endpoints and the exploratory endpoints will only be analyzed using the ITT analysis set. The Safety Analysis Set will be used in the analyses of the safety data.

5.1. Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set will include all subjects in the safety population who had at least 1 post Baseline efficacy evaluation (ie, post Baseline hospitalization, study visit, or date of death). This may also be referred to as a modified intent-to-treat group but for simplicity will be referred to throughout the protocol and SAP as ITT.

5.2. 'Per Protocol' Analysis Set

The per protocol (PP) analysis set will include all subjects in the ITT set who did not violate inclusion/exclusion criteria and who did not have protocol violations considered to impact the interpretation of the primary efficacy analysis.

5.3. Safety Analysis Set

The safety analysis set will include all subjects who are enrolled (randomized) and received at least 1 dose of double-blind medication.

5.4. Other Analysis Sets

No other analysis sets are defined for this study.

5.5. Treatment Misallocations

For subjects, who were not treated, not randomized, or received incorrect treatment, the following rules will be used:

- Randomized but not treated, then they will be excluded from the ITT and PP analysis sets for efficacy evaluations and excluded from the safety analyses as actual treatment is missing.
- Treated but not randomized, then by definition they will be excluded from the efficacy analyses since randomized treatment is missing, but will be reported under the treatment they actually received for all safety analyses.
- Randomized but took incorrect treatment, then they will be reported under their randomized treatment group for all efficacy analyses, but will reported under the treatment they actually received for all safety analyses.

5.6. Protocol Deviations

Below are the protocol deviations that relate to the "Per-Protocol Analysis Set" (Section 5.2).

5.6.1. Deviations Assessed Prior to Randomization

A protocol deviator is a subject who was wrongly enrolled into the study, when inclusion or exclusion criteria were not appropriately satisfied. See Protocol, Section 4.

5.6.2. Deviations Assessed Post-Randomization

Protocol deviations include but are not limited to the following:

- Violations on concomitant medications (see protocol Section 5.5);

- Lack of dosing adherence (level to be defined case by case);
- Dosing errors (eg, treatment misallocation, see Section 5.5 in this SAP);
- Use of diflunisal, tauroursodeoxycholate, and doxycycline during the study.

A full list of protocol deviations will be compiled for the study report prior to database closure. All deviations will be reviewed and a determination of which data to include in the Per-Protocol Analysis Set will be made prior to unblinding the study database.

6. ENDPOINTS AND COVARIATES

6.1. Efficacy Endpoint(s)

6.1.1. Primary Efficacy Endpoint(s)

The primary analysis uses a hierarchical combination applying the method of Finkelstein-Schoenfeld (Finkelstein 1999) to:

- *All-cause mortality, and*
- *Frequency of cardiovascular-related hospitalizations over the duration of the trial, which is defined as the number of times a subject is hospitalized (ie, admitted to a hospital) for cardiovascular-related morbidity.*

6.1.2. Key Secondary Efficacy Endpoint(s)

1. *Change from Baseline to Month 30 in the distance walked during 6-Minute Walk Test (6MWT),*
2. *Change from Baseline to Month 30 in the Kansas City Cardiomyopathy Questionnaire Overall Score (KCCQ-OS).*

6.1.3. Secondary Endpoints

1. *Cardiovascular-related mortality,*
2. *Frequency of cardiovascular-related hospitalization,*
3. *All-cause mortality,*
4. *TTR stabilization at Month 1.*

6.1.4. Exploratory Endpoints

- *Frequency of all-cause hospitalization,*
- *Cardiovascular-related days hospitalized,*
- *All-cause days hospitalized,*

- *All-cause mortality and the frequency of all-cause hospitalization using the Finkelstein-Schoenfeld analysis,*
- *All-cause mortality and cardiovascular-related days hospitalized using the Finkelstein-Schoenfeld analysis,*
- *Cardiovascular-related mortality and frequency of cardiovascular-related hospitalization using the Finkelstein-Schoenfeld analysis,*
- *TTR stabilization at each time points other than Month 1,*
- *TTR concentration at each time point, Change from baseline at time points other than Month 30 in the 6-Minute Walk Test (6MWT),*
- *Change from baseline at time points other than Month 30 in the Kansas City Cardiomyopathy Questionnaire Overall Score (KCCQ-OS),*
- *Change from baseline at each time point in Kansas City Cardiomyopathy Questionnaire: (KCCQ) domain scores (Physical limitation, Symptom stability, Symptom frequency, Symptom burden, Total symptom, Self-efficacy, Social limitation, and Quality of life) and Clinical summary score,*
- *Change from Baseline at each time point in EuroQoL-5 Dimensions (EQ-5D-3L) Index Score and visual analog scale (VAS) scores,*
- *Patient Global Assessment at each time point,*
- *New York Heart Association Classification (NYHA) at each time point,*
- *Change from Baseline at each time point in modified Body Mass Index,*
- *Change from Baseline at each time point in NT-proBNP concentration,*
- *TTR oligomer concentration at each time point,*
- *Change from Baseline at each time point in select echocardiographic parameters, including:*
    - *End-diastolic interventricular septal wall thickness (mm),*
    - *Left ventricle posterior wall thickness (mm),*
    - *Left ventricular ejection fraction (%),*
    - *Left ventricular stroke volume (mL).*
    - *Global Longitudinal Strain,*

[redacted]

- Basal Septal,
- Mid Septal,
- Apical Septal,
- Basal Lateral,
- Mid Lateral,
- Apical Lateral,

- *Circumferential strain basal global,*
- *Circumferential strain mid global,*
- *Circumferential strain apical global,*
- *Radial strain basal global,*
- *Radial strain mid global,*

Radial strain apical global. Additionally, the following echocardiographic parameters will also be measured:

- *Fractional shortening (%),*
- *Left atrial diameter, anterior-posterior (mm),*
- *Left atrial diameter, medio-lateral (mm),*
- *Left atrial diameter, superior-inferior (mm),*
- *Left ventricular end systolic diameter (mm),*
- *Left ventricular end systolic volume (mL),*
- *Left ventricular end-diastolic diameter (mm),*
- *Left ventricular end-diastolic volume (mL),*
- *Left ventricular mass (g),*
- *E/A Ratio,*
- *E/E' Ratio.*

6.2. Safety Endpoints

Safety and tolerability will be assessed with adverse event reporting as well as the conduct of ECGs, clinical laboratory testing, vital signs, and physical examinations.

6.3. Other Endpoints

Not Applicable.

6.4. Covariates

Baseline values will be included as a covariate in the analysis using the mixed model repeated measures (MMRM) model detailed in Section 8.1.3. Where baseline scores are not available (or applicable) for the endpoints (eg, frequency of cardiovascular-related hospitalization), the NYHA baseline classification (NYHA Classes I and II combined and NYHA Class III) will be included in the appropriate models to address baseline severity levels.

All subjects who were incorrectly classified during randomization (wrong TTR Genotype or NYHA baseline classification) will be analyzed using the correct TTR Genotype or NYHA baseline classification values.

7. HANDLING OF MISSING VALUES

No imputation will be done for missing cases for the primary analysis based on the Finkelstein-Schoenfeld method. A sensitivity analysis (of the primary) using multiple imputation as described in Appendix 1.4 will be performed. Supplemental analyses of the two key secondary variables will group the subjects on the basis of their dropout or missing-data patterns using a pattern mixture model described in Section 8.2.2. For all analyses using mixed model repeated measures, no imputation of missing values will be done.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

8.1.1. Finkelstein-Schoenfeld Analyses

The test is based on the principle that each subject in the clinical study is compared to every other subject within each stratum in a pair-wise manner. The method recognizes the higher importance of all-cause mortality. The pair-wise comparison proceeds in hierarchical fashion using all-cause mortality first, assigning a +1 to the "better" subject and a -1 to the "worse" subject (Appendix 1.1). A score, u_{ij}, represents the pair wise comparison and indicates whether patient i has the more favorable outcome than patient j. The "cardiovascular- related hospitalization" in all analyses, unless otherwise specified, will combine hospitalizations adjudicated as cardiovascular-related with hospitalizations adjudicated as indeterminate.

- *If both subjects are dead, then the subject with a longer survival time is assigned +1.*

- *If one subject is alive and the other is not, the live subject receives a +1 and the deceased one a -1.*

- *If both subjects are alive, the comparison uses cardiovascular-related hospitalization to assign scores. The subject with the fewer cardiovascular related hospitalization (frequency) receives a +1 while the other receives -1.*

The test statistic is based on the sum of these scores and will be stratified by TTR genotype (variant and wild-type) and NYHA baseline classification (NYHA Classes I and II combined and NYHA Class III) resulting in a total of 4 strata (2 x 2).

The term "censored" refers to a subject who discontinues from the trial for reasons other than death. For such subjects, there will be additional follow-up to obtain vital status (and transplant status / cardiac mechanical assist device status) at Month 30 and that information will be used in the analysis. In the case where one subject is censored before a second subject has died, and where the vital status of the first patient at Month 30 is missing, then the frequency of cardiovascular-related hospitalizations at the shorter of their follow-up times (the shorter of the 2 subjects' study participation) will be used in assigning a +1 or -1. In the simpler case where one subject drops out but both are known to be alive at Month 30, the frequency of cardiovascular-related hospitalizations, at the shorter of their follow-up times (the shorter of the 2 subjects study participation), will be used in assigning a +1 or -1. Comparisons of cardiovascular related hospitalization frequency for subjects who completed all 30 months study duration will be based on the earlier of the two actual study durations (days).

Subjects, who discontinue for transplantation (ie, heart transplantation and combined heart and liver transplantation) or for implantation of a cardiac mechanical assist device, will be handled in the primary analysis in the same manner as death. More specifically, the time of the transplant or cardiac mechanical assist device implant will be used in the subject-to-subject comparison in the same manner as if the subject had died at that time (regardless of any additional vital status follow-up information). Data from subjects who drop out for a liver-only transplantation will be handled in the same manner as the data from all other censored subjects.

The proposed test is a score test based on the sum of the scores for the treated group. A value of D_i =1 for subjects in tafamidis and D_i =0 for subjects in the placebo group. Using the u_{ij} for every pair of subjects defined above, we assign a score to each subject.

The subjects are divided into 4 strata k =1; 2; 3, 4. If $A_k$is the set of indices of the n_k subjects in the k^{th} strata and that U_i is calculated within strata (for $i \in A_k$; $U_i = \sum_{j \in A_k} u_{ij}$), then the test statistic is based on

$$T = \sum_k \sum_{i \in A_k} D_i \, U_i$$

Let $m_k$be the total number of subjects in the k_{th} stratum who are in the tafamidis group. Then in k_{th} strata

$$E(D_i) = m_k/n_k \text{ and}$$

$$cov\,(D_i, D_j) = \frac{m_k(n_k - m_k)}{(n_k - 1)n_k^2} \quad (\delta_{ij} n_k - 1),$$

where δ_{ij} is the Kronecker delta (valued as 1 if $i = j$ and 0 otherwise).

Since $\sum_{i \in A_k} U_i = 0$ this implies that the mean of T is zero and its variance is

$$V = \sum_k \frac{m_k(n_k - m_k)}{n_k(n_k - 1)} \left(\sum_{i \in A_k} U_i^2\right).$$

The hypothesis of interest is tested by comparing $T/\sqrt{V}$ to the normal distribution.

In the event there is insufficient information for the adjudication process to classify either a mortality or hospitalization as cardiovascular related or not cardiovascular related, then the event will be classified as "indeterminate". In the adjudication process, cases with at least some information indicating a contributory cardiovascular cause, including ambiguous cases, will be adjudicated to the cardiovascular-related category. The test statistic for the "by TTR Genotypes" subgroup analysis will be stratified by NYHA baseline classification (NYHA Classes I and II combined and NYHA Class III). The test statistic for the "by NYHA classifications" subgroup analysis will be stratified by TTR Genotype (variant and wild-type). Subjects who were incorrectly classified during randomization (wrong TTR Genotype or NYHA baseline classification) will be analyzed using the correct TTR Genotype or NYHA baseline classification values.

8.1.2. Survival Analyses

Time to event endpoints including all-cause mortality, and cardiovascular-related mortality will be analyzed using SAS Proc Lifetest; p-values will be from the log-rank test. For cardiovascular-related mortality, subjects who died for reasons other than cardiovascular (including "inderterminate") will be designated as censored at the time of death. Subjects who discontinue for transplantation (ie, heart transplantation and combined heart and liver transplantation) or cardiac mechanical assist device will be handled in the same manner as death (as done in the primary analysis).

Kaplan-Meier survival curves for each treatment group along with median survival times (if applicable) will be presented. Kaplan-Meier product limit estimators will be generated. The number of subjects at risk, number of events and number of censored observations through 6, 12, 18, 24, 30 months will be summarized using the "Method=Life" option in PROC LIFETEST.

Time to event endpoints will also be analyzed using Cox proportional hazards model using Proc PHREG with treatment, TTR genotype (variant and wild-type), and NYHA baseline classification (NYHA Classes I and II combined and NYHA Class III) as factors.

For the analyses by NYHA baseline classification, the Cox proportional hazard model will include treatment and TTR genotype. For the analyses by TTR genotype, the model will include treatment and NYHA baseline classification. The Kaplan-Meier survival curves will also be generated for the analyses by NYHA baseline classification and TTR genotype.

8.1.3. Mixed Model Repeated Measures (MMRM) Analyses

The endpoints evaluated at multiple time points will be analyzed *using a mixed model repeated measures ANCOVA (MMRM) with an unstructured covariance matrix (or as appropriate); center and subject-within-center as random effects; treatment, visit, TTR genotype (variant and wildtype), and visit-by-treatment interaction, as fixed effects and Baseline score as covariate.* While the NYHA baseline classification may serve as an indicator of baseline severity, the endpoints that are evaluated at baseline (and at multiple points post-baseline) will use their respective baseline scores as the appropriate covariate for the MMRM analysis described above.

For the analyses by TTR genotype, the same model specified above will be used, with the addition of terms for TTR genotype-by-treatment interaction and TTR genotype-by-treatment-by-visit 3–way interaction. Similarly for dose, the same model specified above will be used with replacement of "dose" for "treatment". Appropriate CONTRAST statements will be used to generate the LSMEANS from the MMRM model (eg, for dose, 20 mg vs placebo and 80 mg vs placebo) at each post-baseline study visit. The subgroup analysis by NYHA baseline classification (NYHA Classes I and II combined and NYHA Class III) will be done using ANCOVA (MMRM) with an unstructured covariance matrix (or as appropriate); center and subject-within-center as random effects; treatment, visit, TTR genotype (variant and wildtype), NYHA baseline classification, visit-by-treatment interaction, NYHA baseline classification-by-treatment interaction, NYHA baseline classification-by-treatment-by-visit 3–way interaction as fixed effects and baseline score as covariate. All the subgroup analyses will be considered exploratory.

8.1.4. ANOVA

Cardiovascular-related days hospitalized and all-cause days hospitalized will be analyzed using an analysis of variance (ANOVA) with treatment, TTR genotype (variant and wild-type), NYHA Baseline classification (NYHA Classes I and II combined and NYHA Class III), treatment-by-TTR genotype interaction, and treatment-by-NYHA Baseline classification interaction terms as factors.

8.1.5. Poisson Regression for Frequencies

Frequency of cardiovascular-related hospitalization and frequency of all-cause hospitalization will be analyzed using Poisson regression analysis with *treatment, TTR genotype (variant and wild-type), NYHA Baseline classification (NYHA Classes I and II combined and NYHA Class III), treatment-by-TTR genotype interaction, and treatment-by-NYHA Baseline classification interaction terms as factors adjusted for treatment duration.*

For the subgroup analyses by NYHA classification (NYHA Classes I and II combined and NYHA Class III), the Poisson regression analysis will have treatment, TTR genotype (variant and wild-type), and treatment-by-TTR genotype interaction terms as factors adjusted for treatment duration.

For the subgroup analyses by TTR genotype, the Poisson regression analysis will have treatment, NYHA baseline classification, and treatment-by- NYHA baseline classification (NYHA Classes I and II combined and NYHA Class III) as factors adjusted for treatment duration.

8.1.6. Cochran-Mantel-Haenszel Test for Proportions

A Cochran-Mantel-Haenszel (CMH) will be used as a test of proportions. For the overall, and analyses by dose(placebo vs 20 mg and placebo vs 80 mg), a Cochran-Mantel-Haenszel test for proportions stratified by TTR genotype and NYHA baseline severity (NYHA Classes I and II combined and NYHA Class III) will be used. For subgroup analysis by TTR genotype, a CMH test for proportions stratified by NYHA baseline severity will be used. The analysis will also be performed separately by Baseline severity using a CMH test for proportions stratified by TTR genotypes (variant and wild-type).

8.2. Statistical Analyses

The number of subjects screened, randomized to the double-blind treatment phase, and completing the study will be summarized. The reason for all discontinuations will be summarized by treatment group. Baseline demographic and other characteristics, including the frequency of specific genotypes will be tabulated for the ITT population. Quantitative variables will be described by standard descriptive statistics (mean, standard deviation, minimum, and maximum), and qualitative variables will be summarized by frequency tables.

Concomitant medications including their preferred term and therapeutic subgroup will be summarized by treatment groups.

The primary analysis and key-secondary endpoints will be analyzed using both ITT and PP Analysis Sets. All other efficacy analyses will be performed on ITT Analysis Set only.

8.2.1. Primary Analysis

The primary analysis uses a hierarchical combination of all-cause mortality and frequency of cardiovascular-related hospitalizations (which is defined as the number of times a subject is hospitalized [ie, admitted to a hospital] for cardiovascular-related morbidity) over the duration of the trial as described in Section 8.1.1. *The primary analysis will combine the subjects in the tafamidis 20 mg and tafamidis 80 mg groups (including subjects in 80 mg group that may have had a dose reduction to 40 mg) into one pooled group. This pooled group (tafamidis) will be compared with the placebo group using the Finkelstein-Schoenfeld method (Finkelstein 1999).*

8.2.2. Key-Secondary Analyses

The key secondary endpoints listed below will be evaluated using a mixed model repeated measures ANCOVA detailed in Section 8.1.3.

1. Change from Baseline to Month 30 in distance walked during the 6MWT;

2. Change from Baseline to Month 30 in KCCQ Overall score.

To maintain the type 1 error rate at or below the specified level, a pre-specified hierarchical order for testing as indicated above will be used to maintain the overall alpha at 0.05 for these two key secondary endpoints. The multiplicity procedure will be applied to the ITT analysis set only.

Statistical significance of the key-secondary analyses is dependent on first achieving statistically significant results in the primary analysis. In this hierarchical approach of key-secondary endpoints, the change from Baseline to Month 30 in distance walked during the 6MWT is first tested at the 0.05 level. If the p-value for the test of 6MWT is ≤0.05, the 2nd variable in the list, the change from Baseline to Month 30 in KCCQ Overall Summary score will be tested at the 0.05 level. If the p–value of the test for 6MWT is >0.05, then statistical significance cannot be achieved for the subsequent test on KCCQ.

Supplemental analyses of the two key secondary variables will be performed to support the robustness of the conclusions drawn. The pattern-mixture analysis will group the subjects on the basis of their dropout or missing-data patterns. 'Patterns' will be defined under the following two cases:

Case 1:

Pattern 1A - all subjects who have provided the key-secondary endpoint (each done separately) data for month 30.

Pattern 1B - all subjects who have not provided the key-secondary endpoint data for month 30.

Case 2:

Pattern 2A - all subjects who have the key-secondary endpoint data (each done separately) for month 15 or beyond.

Pattern 2B - all subjects who do not have key-secondary endpoint data beyond month 15.

The pattern mixture analysis will use a mixed model repeated measures ANCOVA (MMRM) with an unstructured covariance matrix (or as appropriate); center and subject within center as random effects; treatment, visit, TTR genotype (variant and wild-type), pattern, visit by treatment interaction, and treatment by pattern interaction as fixed effects and baseline score as covariate. Sample SAS code is provided in Appendix 1.3.

Exploratory analyses of the key secondary endpoints will include results from the MMRM analysis at each individual time point other than month 30.

Additional exploratory analyses of the key secondary endpoints will include results from the MMRM analysis at each individual time point by dose group (randomized dose group), TTR genotype (variant and wild-type), and NYHA baseline classification. Descriptive statistics overall, by dose, by TTR genotype, and by NYHA baseline classification will be provided for each time point.

Except for the analyses by dose, all analyses of the key-secondary endpoints, including the proposed exploratory analyses of these endpoints will compare the pooled tafamidis group with the placebo group.

8.2.3. Secondary Analyses

The "cardiovascular -related mortality" in all analyses, unless otherwise specified, will combine deaths adjudicated as cardiovascular-related with deaths adjudicated as indeterminate.

The cardiovascular-related mortality and all-cause mortality will be analyzed using survival analysis methods detailed in Section 8.1.2.

Frequency of cardiovascular-related hospitalizations will be analyzed using the Poisson regression analyses detailed in Section 8.1.5.

All the analyses on the secondary endpoints described above will additionally be presented by TTR genotype (variant and wild-type), NYHA baseline classification as well as dose (randomized dose group) and will be considered exploratory.

The proportion of subjects who achieved TTR stabilization in each treatment group at Month 1 will be compared using a Cochran-Mantel-Haenszel test detailed in Section 8.1.6.

A similar test of proportion will be done on TTR stabilization at all other time points and considered exploratory. No subgroup analyses will be done at these other time points.

Except for the analyses by dose group, all analyses of the secondary endpoints, including the proposed exploratory analyses of these endpoints will compare the pooled tafamidis group with the placebo group.

8.2.4. Exploratory Analyses

A supplemental analysis, repeating the methodology of the primary analysis, will only include hospitalizations adjudicated as cardiovascular related and exclude hospitalizations adjudicated as “indeterminate”. *To examine the potential effect of including heart transplantation or cardiac mechanical assist device as “deaths” in the primary analysis, a sensitivity analysis will be performed treating all transplantation or cardiac mechanical assist device in the same manner as any other censored observation. As an additional sensitivity analysis, a multiple imputation analysis will be applied using the method developed by Rubin (Rubin 1987). Combined results will be provided for the primary analysis (ie, using Finkelstein-Schoenfeld) as well as for the separate mortality and morbidity elements.* Details are provided in Appendix 1.4.

An exploratory analysis, using the methodology of the primary analysis, will be repeated by the dose group to which subjects were randomized (tafamidis 20 mg vs placebo and tafamidis 80 mg vs placebo) to explore the effect by dose group.

Exploratory analysis of the secondary endpoint, all-cause mortality will be done by treating all heart transplantation or cardiac mechanical assist device in the same manner as any other censored observation. Exploratory *subgroup analysis using the Finkelstein-Schoenfeld method comparing the pooled tafamidis group and the placebo group, similar to that of the primary analysis, will also be done by the TTR genotype (variant type and the wild-type) and Baseline severity (NYHA Classes I and II combined and NYHA Class III) status.*

To examine the potential effect of region, the primary analysis will be repeated with the inclusion of a factor for region. More specifically, the test statistic will be stratified by TTR genotype (variant and wild-type), baseline severity category (NYHA Classes I and II combined and NYHA Class III), and region (US and Ex-US).

Frequency of All-cause hospitalization will be analyzed using the Poisson regression analyses detailed in Section 8.1.5.

Cardiovascular-related days hospitalized, and all-cause days hospitalized will be analyzed using an analysis of variance (ANOVA) detailed in Section 8.1.4.

An exploratory analysis based on the Finkelstein-Schoenfeld method similar to that of the primary analysis detailed in Section 8.1.1 will be done for combination of variables listed below:

- All-cause mortality and frequency of all-cause hospitalizations,
- All-cause mortality and cardiovascular-related days hospitalized using the Finkelstein-Schoenfeld analysis,
- Cardiovascular-related mortality and frequency of cardiovascular-related hospitalization using the Finkelstein-Schoenfeld analysis.

The exploratory endpoints listed below will be evaluated at each time point post-baseline using a mixed model repeated measures ANCOVA (MMRM) as detailed in Section 8.1.3.

- Change from Baseline in Kansas City Cardiomyopathy Questionnaire: (KCCQ) domain scores (Physical limitation, Symptom stability, Symptom frequency, Symptom burden, Total symptom, Self-efficacy, Social limitation, and Quality of life) and clinical summary score,
- Change from Baseline in EuroQoL-5 Dimensions (EQ-5D-3L) Index Score and visual analog scale (VAS) scores,
- Patient Global Assessment,
- Change from Baseline in Modified Body Mass Index,

- Change from Baseline in NT-proBNP concentration,
- TTR oligomer concentration at each time point,
- TTR concentration at each time point,
- Change from Baseline in echocardiographic parameters:
    - End-diastolic interventricular septal wall thickness (mm),
    - Left ventricle posterior wall thickness (mm),
    - Left ventricular ejection fraction (%),
    - Left ventricular stroke volume (mL),
    - Global longitudinal strain,
    - Circumferential strain mid global,
    - Radial strain mid global.

  All other echocardiographic parameters listed as endpoints in Section 6.1.4 will be analyzed descriptively.

The TTR oligomer concentration and TTR concentration will additionally be analyzed by dose. Descriptive statistics are presented by visit for the NYHA Classification (Class I, II, III, and IV). The number and percent of subjects with an improvement (decrease by at least one classification), those who worsened (increase by at least one classification), and those with no change (same classification) from baseline are presented at each visit using a shift table. A cross-tabulation of baseline severity level and post baseline change level will be presented at each visit for Patient Global Assessment scale.

Plasma concentrations of tafamidis will be summarized with descriptive statistics (n, arithmetic mean, standard deviation, coefficient of variation, geometric mean, median, and minimum and maximum) by dose, visit, and nominal time.

Plasma concentrations of diflunisal will be provided as listings by visit.

8.2.5. Safety Analyses

The safety assessments in the study are listed in Section 6.2. All randomized subjects who receive at least one dose of study treatment will be included in the safety analysis. All adverse events that are observed from the time of first dosing with study medication (at randomization) until the end of study participation will be included in the safety analysis.

All adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by treatment group. The incidence of treatment-emergent adverse events will be tabulated by treatment group and by system organ

class. The incidence of treatment-emergent adverse events will be displayed by severity and attribution. In addition, the incidence of serious adverse events and adverse events that cause withdrawal will be tabulated. All adverse events will be listed.

The effective duration of treatment is determined by the lag time. Any event occurring within the lag time, whether this occurs during a break in treatment or at the end of treatment, is attributed to the corresponding treatment period. A lag of 28 days will be used for this study.

The following 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers. While the AEs will be additionally analyzed by subgroups, the 3-tier approach will only be applied to the overall AE analyses.

> *Tier-1 events: These are pre-specified events of clinical importance and are maintained in a list in the product's Safety Review Plan. This list may be updated as more is understood about the drug.*
>
> *Tier-2 events: These are events that are not tier-1 but are "common". A MedDRA Preferred Term (PT) is defined as a tier-2 event if there are at least 4 in any treatment group.*
>
> *Tier-3 events: These are events that are neither tier-1 nor tier-2 events.*

The analyses of adverse events under the 3-tier approach is considered exploratory. There will be no adjustment for multiple comparisons or stratification factors in the analyses. For tier-1 and tier-2 events, the proportion of AEs observed in each treatment groups will be presented along with the point estimates and associated 95% confidence intervals of the risk difference for the pooled tafamidis group compared with placebo.

For Tier-1 events p-values will be included in the presentations. AEs will be arranged in the output sorted in descending point estimate of the risk difference within system organ class. Footnotes in the outputs will include the methods used to derive any p-values and confidence intervals as per Pfizer standards. The Tier 1 AEs will be analyzed using the approach of Chan and Zhang (1999) who inverted two one-sided tests at half the significance level each for calculating P-values and confidence intervals.

For Tier 2 AEs, both proportion and 95% CIs will be generated using an asymptotic approach (Proc Binomial). A MedDRA PT is defined as a Tier-2 event if there are at least 4 in any treatment group. A cross-industry expert team on safety planning, evaluation and reporting (Crowe et al, 2009) suggests to use the "Rule of 4" to define tier-2 events. The "Rule of 4" says that if a trial has 400 or fewer subjects per group and there are 4 or more subjects with a given MedDRA PT in any treatment group, then that PT will be categorized as a tier-2 event.

For Tier 3 events, simple proportions will be presented.

All clinical laboratory data will be subjected to clinical review, summarized by frequency of events and mean changes from baseline.

All vital sign measurements will be displayed in listings by subject for each sample collection date and time. The measurement taken immediately prior to randomization will be used as the baseline for calculating changes in vital signs.

Centrally over-read ECG variables will be summarized by mean change from baseline to each measurement time for heart rate, PR interval, QRS width, QT interval and QTcB (Bazett's correction) and QTcF (Fridericia correction) values. Additionally, the incidence of categorical increases in QTc intervals will be provided. Categories for QTcF and QTcB are ≥450 msec, ≥480 msec, and ≥500 msec. Categories for QTcF and QTcB as change from baseline are ≥30 msec increase, ≥60 msec increase and ≥75 msec increase. QTcF is considered the primary QTc value as this correction is more appropriate.

All of the analysis on the safety endpoints will compare placebo with each tafamidis dose (20 mg and 80 mg) as well as the pooled group (combined tafamidis 20 mg and 80 mg).

The safety analyses will also be summarized by TTR genotype and NYHA baseline classification. Treatment-emergent adverse events and serious adverse events will be summarized by gender as well.

Summary of Efficacy Analyses

Table 2. Summary of Proposed Efficacy and Safety Analyses

End Point or Assessment	Overall	By dose	Wild-type vs Variant	NYHA Baseline Classification
Primary Analysis				
Primary – FS Method (All-cause mortality and CV Hospitalization)*	x#	x	x	x
Key-Secondary Analyses				
Change from Baseline to Month 30 on the distance walked during 6-Minute Walk Test (6MWT)*	X##	x	x	x
Change from Baseline to Month 30 on the Kansas City Cardiomyopathy Questionnaire Overall Score (KCCQ-OS)*	X##	x	x	x
Secondary Analyses				
Cardiovascular-related mortality	x	x	x	x
Frequency of cardiovascular-related hospitalization	x	x	x	x
All-cause mortality	x	x	x	x
TTR stabilization at Month 1	x	x	x	-
Exploratory Analyses				
TTR stabilization at each time point other than month 1	x	-	-	-
Frequency of all-cause hospitalization	x	-	-	-
Cardiovascular-related Days Hospitalized	x	-	-	-
All-cause Days Hospitalized	x	-	-	-
FS-method – All-cause mortality and frequency of all-cause hospitalization	x	-	-	-
FS-method – all cause mortality + CV-related hosp days	x	-	-	-
FS-method – CV-related mortality + frequency of CV-related hosp	x	-	-	-

End Point or Assessment	Overall	By dose	Wild-type vs Variant	NYHA Baseline Classification
Change from Baseline at each time point on EuroQoL-5Dimensions (EQ-5D-3L) Index Score and visual analog scale (VAS) scores	x	-	-	-
TTR oligomer concentration at each time point	x	x		
TTR concentration at each time point	x	x		
Patient Global Assessment at each time point	x	-	-	-
NYHA classification change from baseline (shift table)	x	-	-	-
Change from Baseline at each time point on Kansas City Cardiomyopathy Questionnaire: (KCCQ) domain scores (Physical limitation, Symptom stability, Symptom frequency, Symptom burden, Total symptom, Self-efficacy, Social limitation, and Quality of life) and clinical summary scores	x	-	-	-
Change from Baseline at each time point on Modified BMI Mass Index	x	-	-	-
Change from Baseline at each time point in Echocardiography (septal and ventricular wall thickness, ejection fraction, and stroke volume, Global longitudinal strain, Circumferential strain mid global, Radial strain mid global)	x	-	-	-
Change from Baseline at each time point on NT-proBNP concentration	x	-	-	-
Change from Baseline at time points other than month 30 on the distance walked during 6-Minute Walk Test (6MWT)	x	-	-	-
Change from Baseline at time points other than month 30 on the Kansas City Cardiomyopathy Questionnaire Overall Score (KCCQ-OS)	x	-	-	-
Additional echocardiographic parameters (listed in Section 6.1.4)	x			
Safety				
AEs labs, Vitals	X	X	X	X

*Analysis will be performed using both ITT and PP Analysis Sets. All other efficacy analysis will be performed on ITT Analysis Set only.

#Sensitivity analysis of the primary analysis will be done as described in Section 8.2.4.

Supplemental analysis of the key-secondary endpoints will be done as described in Section 8.2.2.

9. REFERENCES

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10. APPENDICES

Appendix 1. Statistical Methodology Details

Appendix 1.1. Finkelstein-Schoenfeld Example Scoring Algorithm

Scenario	i/j	All-cause Mortality	Survival Time (from baseline)	Cardiovascular-related hospitalization	Score
1	i	Dead	-	-	-1
	j	Alive	-	-	
2	i	Dead	Low	-	-1
	j	Dead	High	-	
3	i	Dead	Tied	High	-1
	j	Dead	Tied	Low	
4	i	Dead	Tied	Tied	0
	j	Dead	Tied	Tied	
5	i	Alive	-	High	-1
	j	Alive	-	Low	
6	i	Alive	-	Tied	0
	j	Alive	-	Tied	

Subjects that are tied on "all-cause mortality" will be compared by frequency of cardiovascular-related hospitalization. If the 2 subjects have different follow-up times, the smaller of the 2 follow-up times will be used in comparing the frequency of cardiovascular-related hospitalization.

If i and j are reversed in severity than the value assigned to i is +1.

Appendix 1.2. Definition and Use of Visit Windows in Reporting

The following describes the clinical visits windows allowed within the protocol after month 1 visit:

Clinic Visits (Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30) ±2 weeks

End of Study Visit (Month 30) ±2 weeks or Early Study Discontinuation

However, in order to maximize the use of all available data, the visit windows for each visit are expanded as follows:

For endpoints collected every 3 months:

Clinic Visits (Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30) ±6 weeks

All nominal visits (months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30) will use the data as collected from that visit. Early termination visits will never replace an existing visit. If the visit covered by the windowing rules above is already populated with an existing nominal visit, then the early termination visit should be mapped forward to the next 3 month visit.

For endpoints collected every 6 months:

Clinic Visits (Months 6, 12, 18, 24, 30) ±3 months

All nominal visits (months 6, 12, 18, 24, 30) will use the data as collected from that visit. Early termination visits will never replace an existing visit. If the visit covered by the windowing rules above is already populated with an existing nominal visit, then the early termination visit should be mapped forward to the next 6 month visit.

For Echocardiogram collected at months 6, 18, and 30:

Clinic Visits (Months 6, 18, 30) ±6 months

All nominal visits (months 6, 18, 30) will use the data as collected from that visit. Early termination visits will never replace an existing visit. If the visit covered by the windowing rules above is already populated with an existing nominal visit, then the early termination visit should be mapped forward to the next nominal visit.

Appendix 1.3. Sample SAS Code for Analyses Described in Sections 8.1.2 – 8.2.6

Sample SAS code to fit the mixed model repeated measures specified in Section 8.1.3 is given below. The response variable Y is the change from baseline at the study visits.

```
PROC MIXED DATA=xxx METHOD=REML EMPIRICAL;
CLASS pid center trt visit genotype;
MODEL y= ybase trt visit genotype trt *visit;
RANDOM int/SUBJECT=center;

REPEATED visit /SUBJECT= pid (center) r type=UN;

RUN;
```

Sample SAS code for the survival analysis specified in Section 8.1.2 is given below.

```
PROC LIFETEST DATA=xxx PLOTS=(s) graphics;
TIME dur *status(0);
STRATA trt;
RUN;

PROC PHREG DATA=xxx;
MODEL dur*status(0)=trt genotype NYHAbase/ ties=EXACT;
RUN
```

Sample SAS code for the ANOVA specified in Section 8.1.4 is given below.

```
PROC GLM DATA=xxx;
CLASS trt genotype NYHAbase;
MODEL y= trt genotype NYHAbase trt*genotype trt*NYHAbase;
RUN;
```

Sample SAS code for the Poisson regression specified in Section 8.1.5 is given below.

```
PROC DATA=xxx;
ln_styyr=log(styyr);* log transformation to normalize duration of participation ;
RUN;

PROC GENMOD DATA=xxx;
CLASS trt genotype NYHAbase;
MODEL y= trt genotype NYHAbase trt*genotype
trt*NYHAbase/ type 3 dist=poisson link=log offset=ln_styyr;
RUN;
```

Sample SAS code for the CMH test specified in Section 8.1.6 is given below. In the code below, the variable NYHA_GENOTYPE is obtained from combining NYHA baseline classification and TTR genotype into one variable (with 4 levels).

```
PROC FREQ DATA=xx;
TABLES NYHA_GENOTYPE*TRT*STABILIZED / CMH
RUN;
```

Sample SAS code for the pattern mixture analysis specified in Section 8.1.5 is given below.

```
PROC MIXED DATA=xxx empirical;
CLASS pid visit center trt pattern genotype;
MODEL y= ybase visit trt genotype pattern visit*trt
trt*pattern / solution;
random int/subject=center;
repeated visit /subject= pid (center) r type=UN;
ESTIMATE 'Tafamidis vs placebo Month 30'
        trt 1 -1 visit*trt  0 0 0 0 0 0 0 0 1 -1
trt*pattern 0.5 0.5 -0.5 -0.5 /cl e; * Placebo adjusted LSMEANS of Tafamidis
averaged over the pattern (equal weight=0.5);
run;
```

[redacted]

Appendix 1.4. Details of Multiple Imputation Method to be Used in Sensitivity Analysis

For purposes of the missing data sensitivity analyses, the study duration of 30 months will be partitioned into 3 intervals of 10 months each. These will be referred to as period 1, period 2, and period 3, representing months 1-10, 10-20, and 20-30 respectively. Imputation models will be estimated and applied separately for each treatment group. Hospitalizations are not imputed for subjects after their death. The imputation procedure consists of two distinct phases: 1) models for cardiovascular-related hospitalization rates are estimated for each time interval, and 2) these models are then used to impute the number of cardiovascular hospitalizations following censoring (dropout) amongst subjects who dropout in an interval. Dropouts are the only source of missing hospitalization data, so there will be a monotone missing data pattern. The two-stage multiple imputation process developed here follows the procedure for monotone missing data in Rubin (1987).

Within each short time interval (10 months), a Poisson regression model with a constant rate will be assumed for hospitalization counts. No imputation is required for a patient who dies during the interval. Because the model applies only to subjects who survive the interval, and subjects who die during the interval are likely to have differing hospitalization rates, subjects who die in an interval will be excluded from the imputation model estimation. All other subjects still in the study at the beginning of the interval are included in the model estimation. The reduced exposure of dropouts during the intervals is represented by an exposure multiplier (between 0-10) of the monthly hospitalization rate (McCullagh and Nelder, 1989). The monthly hospitalization rate during the first period is a function of the baseline covariates NHYA baseline classification and TTR genotype. The monthly hospitalization rate during the second period is a function of the baseline covariates and the hospitalization counts during the first period. The monthly hospitalization rate during the third period is a function of the baseline covariates, and the hospitalization counts during the first and second periods.

PROC GENMOD will be used to compute maximum likelihood estimates (MLE) of the parameters of the Poisson regression model. It will also be used to compute the variance-covariance matrix for the estimates from each time period. A total of 1000 imputed data sets will be generated. To account for estimation error when forming the imputed data sets, 1000 independent sets of the Poisson model parameters will be generated for each time period from a multivariate normal distribution with mean equal to the MLE, and with the variance-covariance matrix equal to the MLE variance-covariance matrix. The i^{th} set of Poisson model parameters from each time period are paired together, yielding 1000 sets of parameters for generating the 1000 imputed data sets. For each iteration, the individual patient Poisson rate (lambda) will be generated using the Poisson regression coefficient estimates for that iteration.

The imputation process described here is applied with each set of Poisson model parameters. Subjects without complete data are comprised of two types: those with no participation during the period, and those with partial participation during the period. For those with no participation, the prediction equation will be used to impute a hospitalization count for the entire period. For those with partial participation, the prediction model will be applied to impute a hospitalization count appropriate for the remainder of the period after the patient

dropped out. The imputed value will be added to the actual observed value for that patient from the part of the period prior to their dropping out. For example, consider a patient who drops out at month 5. The patient's Period 1 imputed value will be the sum of their actual hospitalization count from month 1 to month 5 added to the predicted value from month 5 to month 10.

Any missing data are imputed sequentially beginning with the first time period, then the second and third periods. The imputation model during the first period depends only on fully observed baseline covariates. The imputation model during the second period also depends on the hospitalization count during the first period. For any patient who dropped out during the first period, their imputed count in the first period is used in the model to produce the imputed value for that subject in period 2. Note that this differs from the process when estimating the imputation model (Rubin, 1987). A similar procedure is applied for imputation of missing values during period 3. Finally, the hospitalizations for each patient are summed to generate a complete 30-month (imputed) CV hospitalization frequency.

The null hypothesis will be tested based on the 1000 imputed data sets by computing the components of the complete-data Finkelstein-Schoenfeld statistic to yield 1000 numerator values, and 1000 denominator values (square root of the numerator variance). Following Rubin (1987), the numerators will then be averaged. The variance of this average will be the average within-imputation variance computed from the 1000 complete-data variances of the numerators combined with the between imputation variability in the numerators to yield a normal Z-statistic. The 1000 imputed hospitalization data sets will also be used to summarize hospitalization rates in the treatment groups.

Sample SAS Code

Poisson model specified below will be used to fit cardiovascular hospitalization data and will then be used to impute the missing data. The model will be fit separately for each of the 3 periods and will be done separately for both treatment groups (placebo and pooled tafamidis). Only the subjects that entered a given period (not completely missing during the period) will be used in determining the model. The "OFFSET" in the linear model implemented by PROC GENMOD is the adjustment for the exposure time in the interval (those who entered the period but did not complete the 10 months). The variable "months_exposure", used in the "OFFSET", is a log transformation of the months of exposure in a given period.

```
proc genmod data = nonmissingperiod1; ;* Only includes subjects with non-missing count
data for period 1;
class NYHAnum MUTATIONnum;
model count = NYHAnum MUTATIONnum /dist=p link=log offset=months_exposure
;*model terms for period1;
output out=predpoi p=p;
run;
```

proc genmod data = nonmissingperiod2; ;* Only includes subjects with non-missing count data for period 2;
class NYHAnum MUTATIONnum;
model count = countbase1 NYHAnum MUTATIONnum /dist=p link=log offset=months_exposure*; *model terms for period 2 where countbase1 is CV hospitalization count from period 1;*
output out=predpoi p=p;
run;

proc genmod data = nonmissingperiod3;* Only includes subjects with non-missing count data for period 3;
class NYHAnum MUTATIONnum;
model count = countbase1 countbase2 NYHAnum MUTATIONnum /dist=p link=log offset=months_exposure*; * model terms for period 3 where countbase1 and countbase2 are CV hospitalization counts from period 1 and 2 respectively;*
output out=predpoi p=p;**run**;

The macro below can be used to perform the multiple imputation. The variable "seedval" will be the starting seed and the variable "numimp" will specify the number of multiple imputations to be performed. The dataset "withmissing" will contain all the subjects that will be imputed.

%macro impute (output, seedval, numimp);
data &output;
set withmissing;
seed=&seedval;
do MInum = **1** to &numimp;
lambda= exp(± **x.xx** ± x.xxx countbase(varies depending on the period) ± **x.xx** *NYHAnum ± x.xx*MUTATIONnum);
count = ranpoi(seed, lambda); * *coefficients will be randomly generated from a normal distribution based on the estimates and standard error output from PROC GENMOD;*
output;
end;
run;
%mend impute;

The macro input statement will use a seed value of 999 and perform 1000 multiple imputations.

%***impute*** (impute2, **999**, **1000**);