Protocol B3461045

A PHASE 3 MULTICENTER, OPEN-LABEL , STUDY TO EVALUATE THE SAFETY OF DAILY ORAL DOSING OF TAFAMIDIS MEGLUMINE (PF-06291826-83) 20 MG OR 80 MG [OR TAFAMIDIS (PF-06291826-00) 61 MG] IN SUBJECTS DIAGNOSED WITH TRANSTHYRETIN CARDIOMYOPATHY (ATTR-CM)

Statistical Analysis Plan
(SAP)

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1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for Study B3461045 is based on the protocol global amendment 4 dated 09 August 2019 and United States specific PACL dated November 26, 2019.

SAP Version	Change	Rationale
1	Not Applicable	Not Applicable
2	Changes are captured in the summary of changes table (Table 1)	Amendment to make minor corrections to the SAP
3	Amended to reflect the protocol amendment 3. Changes are captured in summary of major changes table (Table 1)	Amended to reflect the protocol amendment 3
4	Amended to reflect the protocol amendment 4. Changes are captured in summary of major changes table (Table 1)	Amended to reflect the protocol amendment 4
5	Added analyses of select endpoints excluding data from site 1121 (all subjects) to address a potential quality event identified at the site.	Amended to add analyses to address a potential quality event identified at site 1121

Table 1. Summary of Major Changes in SAP Amendments

Amendment 1 (Version 2)

Section of the SAP	Summary of Change	Rationale
3.3. Other Endpoints	Updated KCCQ related domain and summary scores	Updated to be consistent with the developers' names for the KCCQ domain and summary scores
3.4. Baseline Variables	Updated "Day 0", the screening visit as the baseline for all endpoints in study B3461045, except for mortality- based and KCCQ endpoints	Updated to accurately reflect "Day 0" as baseline vs "Day 1"
4.4. Other Analysis Sets	Added definition of "Combined Mortality Analysis Set"	Will be used to conduct mortality based analyses on combined mortality data across studies B3461028 and its extension B3461045
6.1.1. All-cause Mortality	Clarified that analysis will be done using "Combined Mortality Analysis Set"	Updated to clarify the analysis set to be used in all-cause mortality analysis
6.1.1. All-cause Mortality	Added sensitivity analysis treating subjects with heart transplantation or cardiac mechanical assist device as censored subjects	Added sensitivity analysis of the all-cause mortality analysis
6.1.1. All-cause Mortality	Clarified the "Placebo/Tafamidis" as the comparator arm in the "by –dose" analysis of mortality based endpoints	Subjects that received placebo in the parent and were never enrolled in the extension study cannot be included in "placebo/20mg" or "placebo/80 mg" group. The pooled "Placebo/Tafmidis" group will be used as the comparator arm in the "by-dose" analysis of mortality based endpoints
6.2. Other Endpoint(s)	Updated to clarify how data collected as part of the country-specific amendment (Amendment 1) will be handled.	Updated to clarify how data at Month 3 collected as part of country-specific amendment will be handled.
6.2.3. Kansas City Cardiomyopathy Questionnaire	Updated KCCQ related domain and summary scores	Updated to be consistent with the developers' names for the KCCQ domain and summary scores
Appendix 1. SUMMARY OF ANALYSES	Updated KCCQ related domain and summary scores	Updated to be consistent with the developers' names for the KCCQ domain and summary scores

Amendment 2 (Version 3)

Section of the SAP	Summary of Change	Rationale
2.1. Study Objectives	Updated objective to reflect addition of Cohort B and to be consistent with protocol amendment	Updated objective to be consistent with protocol amendment
2.2. Study Design	Updated study design section to reflect the addition of Cohort B, transition of all subjects to open label 61 mg dose (where available), and to update the study flow chart to be consistent with protocol amendment	Updated study design section to be consistent with protocol amendment
3.4. Baseline Variables	Updated to add definition of baseline values for Cohort B	Updated to add definition of baseline values for Cohort B
3.5.1 Adverse Events	Updated definition of treatment-emergent adverse event	Updated the definition to add more clarity
4.3. Safety Analysis Set	Updated to reflect addition of Cohort B and removed reference to mortality related analyses	Updated to reflect addition of Cohort B. Sentence referencing mortality based analyses was removed after adding more text to Section 4.4 "Other Analysis Sets" clarifying the subjects who will be used in analyzing mortality related analyses
4.4. Other Analysis Sets	Updated to clarify the definition of "Combined Mortality" Analysis Set", and indicate this analysis set will only be used for time to event analyses of Cohort A	Updated to clarify the definition of "Combined Mortality" Analysis Set", and indicate this analysis set will only be used for time to event analyses of Cohort A
5. GENERAL METHODOLOGY AND CONVENTIONS	Updated to clarify the timing of the final analysis with respect to subjects that withdraw from the study due to commercial access to prescription	Updated to clarify the timing of the final analysis
5.1. Hypotheses and Decision Rules	Updated to reflect addition of Cohort B and added clarity on the type I error rate to be used and rationale for not having multiplicity adjustment	Updated to reflect addition of Cohort B and added clarity on the type I error rate to be used and rationale for not having multiplicity adjustment
5.2. General Methods	Updated to clarify that all summaries for Cohort A will be presented using "Tafamidis/Tafamidis" and "Placebo/Tafamidis" and "by dose" summaries are removed	Since all Cohort A subjects will be on 61 mg free acid soft gel capsule, analyses by dose are not relevant and therefore removed

Section of the SAP	Summary of Change	Rationale
6.1.1. All-cause Mortality	Updated to reflect the addition of Cohort B and removed "by dose" analyses for Cohort A subjects	Updated to reflect the addition of Cohort B and all subjects in Cohort A moving to the 61 mg free acid formulation
Sections 6.2.1. Cardiovascular-related mortality, 6.2.2. Hospitalization, 6.2.3. Kansas City Cardiomyopathy Questionnaire, 6.2.4. New York Heart Association, 6.2.5. Body Mass Index/modified Body Mass Index, 6.3. Subset Analyses, 6.4. Baseline and Other Summaries and Analyses, 6.5. Safety Summaries (including other endpoints)	Updated to reflect the addition of Cohort B and indicate descriptive summaries will be provided separately for Cohorts A and B	Updated to reflect the addition of Cohort B
Section 6.2.3	Added center and subject-within-center as random effect to the repeated measures model	Added center random effect to align the model description with the SAS code in the appendix and also the model used in study B3461028
Section 6.3, and Appendix 1 Summary of Analyses	Removed references to "pooled treatment group"	"pooled treatment group" was used in the prior versions of the SAP referring to "Tafamidis/Tafmidis" and "Placebo/Tafamidis"groups and was used to distinguish these groups from "by dose" analyses treatment groups. The "by dose" analyses are removed in this amendment and therefore the references to "pooled treatment group" are also removed
Appendix 1. SUMMARY OF ANALYSES	Updated to reflect addition of Cohort B and removed "by dose" summaries	Updated to reflect addition of Cohort B and removed "by dose" summaries

Amendment 3 (Version 4)

Section of the SAP	Summary of Change	Rationale
3.3. Other Endpoints	Updated to reflect the addition of NT-proBNP and Troponin I	Updated to be consistent with protocol amendment 4
3.4. Baseline Variables	Updated to specify the definition of baseline for NT-proBNP and Troponin I	Updated to specify the definition of baseline for NT-proBNP and Troponin I
5.3. Methods to Manage Missing Data	Clarify that missing data from Cohort A subjects who ended participation in the study and returned subsequently will not be imputed	Updated to reflect the protocol administrative letter (PACL) issued on November 26, 2019 allowing Cohort A subjects who ended participation to return to the study
6.2.3. Kansas City Cardiomyopathy Questionnaire	Clarified the treatment groups to be used in the analysis of KCCQ related endpoints	Updated to clarify the treatment groups to be analyzed
6.2.6. NT-proBNP and Troponin I	Specific analyses for the 2 endpoints (NT-proBNP and Troponin -I) added in protocol amendment 4	Updated to be consistent with protocol amendment 4
6.5.1. Adverse Events	Clarify how adverse events from Cohort A subjects who ended participation in the study and returned subsequently will be handled	Updated to reflect the protocol administrative letter (PACL) issued on November 26, 2019 allowing Cohort A subjects who ended participation to return to the study.
Section 9. APPENDICES	Summary of analyses table in Appendix 1 and definition and use of visit windows in reporting in Appendix 1.1. updated to reflect the addition of NT-proBNP and Troponin I	Updated to be consistent with protocol amendment 4

Amendment 4 (Version 5)

Section of the SAP	Summary of Change	Rationale
Various Sections listed below. 2.1. Study Objectives 3.3. Other Endpoints 3.4. Baseline Variables 4.4. Other Analysis Sets 6.2.1. Cardiovascular-related mortality	Removed extra spaces and/or updated text to correct typos	Removed extra spaces and/or updated text to correct typos

Section of the SAP	Summary of Change	Rationale
6.3. Subset Analyses 6.4. Baseline and Other Summaries and Analyses 6.5.1. Adverse Events Appendix 1.1. Definition and Use of Visit Windows in Reporting		
6.5.2. Laboratory Data	Added analyses of laboratory data excluding site 1121	Updated to address a potential quality issue at site 1121
6.5.4. Physical Examinations and Vital Signs	Added analyses of vital signs data excluding site 1121	Updated to address a potential quality issue at site 1121
Appendix 1.1. Definition and Use of Visit Windows in Reporting	Added a paragraph describing calculation of visit windows for KCCQ, NT-proBNP, Troponin I endpoints	KCCQ, NT-proBNP, Troponin I analyses will combine data from B3461028. Clarification was provided on how visit windows will be re-calculated for all study visits from B3461045

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study B3461045. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives

Primary Objectives:

- *To obtain additional, long-term, safety data for tafamidis in subjects with transthyretin amyloid cardiomyopathy (ATTR-CM).*
- *To provide investigational product, tafamidis, to enrolled subjects until local availability by prescription for the ATTR-CM indication.*

2.2. Study Design

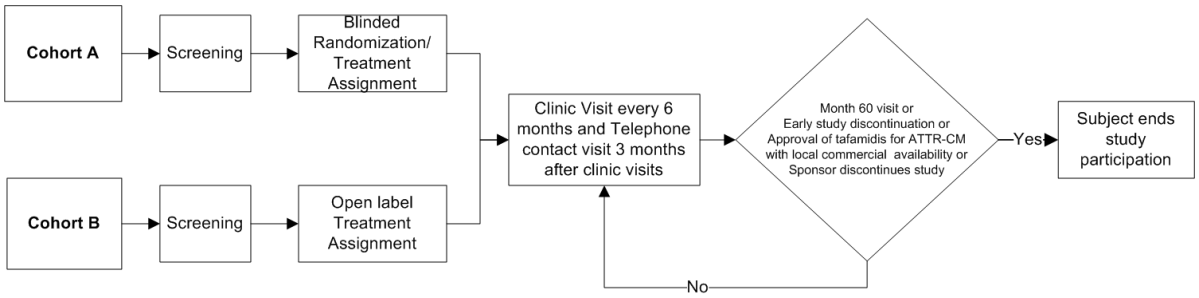
This is a Phase 3, open-label long-term extension safety study designed to obtain additional safety data for tafamidis meglumine 20 mg and 80 mg (or tafamidis 61 mg where available), and to continue to provide enrolled subjects with tafamidis for up to 60 months, or until subject has access to tafamidis for ATTR-CM via prescription, whichever occurs first. The study will also end before 60 months if the sponsor discontinues the study. Subjects withdrawn from the study due to commercial access to prescription tafamidis in their

respective countries will be considered study completers. The decision to withdraw subjects for transition to commercial tafamidis will be made by the sponsor.

Eligible study participants will be enrolled in 2 Cohorts:

- *Cohort A – Subjects diagnosed with ATTR-CM who completed 30 months of participation in Study B3461028.*
- *Cohort B – Subjects diagnosed with ATTR-CM who have not previously participated in Study B3461028.*

Figure 1. Flowchart of Study Participation



Cohort A subjects *receiving tafamidis meglumine 20 mg or 80 mg will be assigned to tafamidis 61 mg, once daily, in addition to standard of care (eg, diuretics), for up to 60 months. Subjects will be assigned to tafamidis meglumine 80 mg in regions where 61 mg tafamidis is unavailable.*

At enrollment, subjects in Cohort B will be assigned to open label 61 mg tafamidis once daily, in addition to standard of care (eg, diuretics), for up to 60 months. One dose reduction to 20 mg tafamidis meglumine will be permitted for adverse events related to tolerability. Subjects will be assigned to 80 mg tafamidis meglumine in regions where 61 mg tafamidis is unavailable.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

Safety as measured by:

- *All-cause mortality.*
- *Incidence of treatment-emergent adverse events.*

3.2. Secondary Endpoint(s)

Not Applicable.

3.3. Other Endpoints

- *Cardiovascular-related mortality.*
- *Frequency of all-cause hospitalization.*
- *Frequency of cardiovascular-related hospitalization (including heart failure, arrhythmia, myocardial infarction, stroke and other cardiovascular-related events).*
- *Change from baseline at each visit in Kansas City Cardiomyopathy Questionnaire Overall Score and domain scores (Physical limitation, Symptom stability, Symptom frequency, Symptom burden, Total symptom, Self-efficacy, Social limitation, and Quality of life) and Clinical summary score.*
- *New York Heart Association classification at each visit.*
- *Change from baseline in Body Mass Index/modified Body Mass Index at each visit.*
- *Change from baseline in N-terminal pro-hormone brain natriuretic peptide (NT-proBNP) concentration at each visit.*
- *Change from baseline in Troponin I concentration at each visit.*
- *Assessment of physical examinations, use of concomitant medications, electrocardiograms (ECGs), clinical laboratory testing, vital signs at each visit.*

3.4. Baseline Variables

Cohort A Subjects: In the analyses of Cohort A subjects, for all endpoints except for all-cause and cardiovascular-related mortality,KCCQ, NT-proBNP, and Troponin I, Day 0 of the subjects participation in Study B3461045 will be used as baseline.

For time to event endpoints, ie, all-cause mortality and cardiovascular related mortality, the data from Study B3461028 will be included in the time to event analysis. Therefore, the baseline for Study B3461028 will be used as the start time in the time to event analyses.

Table 2. Summary of Definition for Baseline Values

Endpoints	Baseline Definition
All endpoints except for mortality, KCCQ, NT-proBNP, Troponin I	Last observation prior to the subject receiving B3461045 study treatment.
All-cause and cardiovascular-related mortality,KCCQ (overall and domain scores), NT-proBNP, Troponin I	Study day corresponding to baseline measurement in the preceding double-blind study B3461028 will be used as the start time in all the mortality based analysis and as baseline for the KCCQ based endpoints (overall, domain, and clinical summary scores), NT-proBNP, Troponin I

Cohort B Subjects: In all the analyses of Cohort B subjects, Day 0 of the subjects participation in Study B3461045 will be used as baseline.

3.5. Safety Endpoints

3.5.1. Adverse Events

An adverse event is considered treatment emergent in study B3461045 if:

- The event occurs during the "effective duration of treatment" (defined in Section 6.5.1) in Study B3461045 and was not seen prior to the start of treatment in the study B3461045, or
- The event was observed prior to the start of study B3461045 but increased in severity during treatment in Study B3461045.

4. ANALYSIS SETS

4.1. Full Analysis Set

Not Applicable.

4.2. Per Protocol Analysis Set

Not Applicable.

4.3. Safety Analysis Set

The safety analysis population consists of all subjects (Cohorts A and B) who are enrolled in this study and who have taken at least one dose of study treatment.

4.4. Other Analysis Sets

The "Combined Mortality Analysis Set" will include all subjects in the ITT-Analysis Set from B3461028. Mortality analyses in study B3461045 for Cohort A subjects will combine data from subjects in study B3461028, including subjects who died, discontinued in B3461028, or didn't enroll into B3461045 (ie, ITT Analysis Set from B3461028) with mortality data through participation in the B3461045 study. This analysis set will be referred to as "Combined Mortality Analysis Set".

5. GENERAL METHODOLOGY AND CONVENTIONS

The final analysis will be performed when all the subjects enrolled into the the study either discontinue (including deaths), or complete the study (60 months), or withdraws from the study due to commercial access to prescription tafamidis. Note that subjects withdrawn from the study due to commercial access to prescription tafamidis in their respective countries will be considered study completers. The study will also end before 60 months if the sponsor discontinues the study. Interim analyses may also be performed during the course of the study to allow for the reporting of data to the scientific community.

5.1. Hypotheses and Decision Rules

The primary objective of the study is to obtain additional, long term, safety data for tafamidis in subjects with transthyretin cardiomyopathy (ATTR-CM) and to provide investigational product, tafamidis, to ATTR-CM subjects who complete 30 months of blinded treatment on protocol B3461028 (Cohort A) and to Subjects diagnosed with ATTR-CM who have not previously participated in Study B3461028 (Cohort B). Therefore, only limited hypothesis testing ie, mortality and change from baseline in KCCQ for Cohort A subjects will be performed. All hypothesis testing will be conducted using two-sided tests with alpha = 0.05 level of significance. Since the primary objective of the study is to collect safety information, no multiplicity adjustment will be done. No hypothesis testing will be done on Cohort B subjects.

5.2. General Methods

For Cohort A, analyses will be performed using tafamidis/tafamidis and placebo/tafamidis treatment groups. Subjects randomized to tafamidis in parent study B3461028 and continue on tafamidis in the extension study B3461045 will be grouped as tafamidis/tafamidis. Subjects randomized to placebo in study B3461028 and randomized to tafamidis in the extension study B3461045 will be grouped as placebo/tafamidis.

For Cohort B, since subjects in this Cohort will all be administered the same dose, only overall descriptive statistics will be provided.

5.3. Methods to Manage Missing Data

Other than standard approaches for missing dates for adverse events, no data imputation will be performed in the study. Missing data from Cohort A subjects who ended participation in B3461045 study without achieving the completion criteria of sustainable access to tafamidis by prescription, and allowed to return to the study and continue participation until they reach protocol defined study completion will not be imputed. Adverse events reported in the CRF that occurred between the time a subject ended the participation and subsequently returned will be evaluated for treatment-emergence in the same manner as adverse events that occurred during the study participation.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. All-cause Mortality

For Cohort A subjects, time to all-cause mortality will be calculated from Day 1 of the Study B3461028 based on the “Combined Mortality Analysis Set” as defined in Section 4.4. All-cause mortality will be analyzed using SAS Proc Lifetest; p-values will be from the log-rank test. Kaplan-Meier survival curves for each treatment group along with median survival times (if applicable) will be presented comparing tafamidis/tafamidis group with placebo/tafamidis group.

All-cause mortality will also be analyzed using Cox proportional hazards model with treatment, NYHA baseline classification, and TTR genotype (variant and wild-type) as factors. 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 same manner as death. 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.

To examine the potential effect of including heart transplantation or cardiac mechanical assist device as "deaths" in the all-cause mortality analysis, a sensitivity analysis will be performed treating all transplantation or cardiac mechanical assist device in the same manner as any other censored observation.

For Cohort B, since subjects in this Cohort will all be administered the same dose, only overall descriptive statistics will be provided. Kaplan-Meier survival curve along with median survival time (if applicable) will be presented.

6.2. Other Endpoint(s)

As a general rule, data from endpoints that are collected at "Month 3" either in France or Germany as part of the country-specific protocol amendment will be included in study listings and will be summarized descriptively at that time point but will not be included in any inferential analyses. Data at Month 3 from one or two countries will be limited and could lead to convergence issues for the models used in the inferential analyses.

6.2.1. Cardiovascular-related Mortality

For both Cohort A and B, cardiovascular-related mortality will be analyzed separately similar to all-cause mortality detailed in Section 6.1.1. Cardiovascular relatedness will be based on an evaluation and clinical judgment of the MedDRA preferred terms.

6.2.2. Hospitalization

The frequency (annualized rate) of all-cause and cardiovascular-related hospitalizations during the study will be summarized descriptively separately for Cohort A and B. Cardiovascular relatedness will be based on an evaluation and clinical judgment of the MedDRA preferred terms.

6.2.3. Kansas City Cardiomyopathy Questionnaire

The KCCQ will be summarized by the following summary scores calculated using the guidelines established in the KCCQ scoring instructions from the developer:

Physical limitations	*Self-efficacy*
Symptom stability	*Quality of life*
Symptom frequency	*Social limitation*
Symptom burden	*Overall summary score*
Total symptom score	*Clinical summary score*

For Cohort A, the overall, domain, and clinical summary scores will be evaluated as a change from baseline at each visit using a MMRM (repeated measures mixed model) with an unstructured covariance matrix (or as appropriate) with center and subject-within-center as a random effects and treatment (tafamidis/tafamidis and placebo/tafamidis), visit, TTR genotype (variant and wild- type), and visit-by-treatment interaction, as fixed effects and baseline score as covariate. *Data will also be summarized by each scheduled assessment.*

As defined in Section 3.4, the baseline for Study B3461028 will be used as the baseline for all KCCQ based analyses. All visits from Study B3461028 will also be included in the repeated measures model described above.

For Cohort B, descriptive statistics for change from baseline at each post-baseline visit will be provided.

6.2.4. New York Heart Association

For Cohorts A and B, subjects will be evaluated using the New York Heart Association (NYHA) classification. Descriptive statistics (frequency) will be presented by clinic visit for each classification: Class I, Class II, Class III, and Class IV. The number and percentage of subjects who improved, worsened, or with no change from baseline will also be presented at each visit via a shift table.

6.2.5. Body Mass Index/modified Body Mass Index

For Cohorts A and B, BMI and mBMI values at each visit and change from baseline will be presented in summary tables and data listings. Descriptive statistics will be provided by visit.

6.2.6. NT-proBNP and Troponin I

For Cohort A, as defined in Section 3.4, the baseline for Study B3461028 will be used as the baseline for all NT-proBNP and Troponin I based analyses. Change from baseline for all visits, including the visits from Study B3461028 will be summarized descriptively for NT-proBNP and Troponin I by treatment group (tafamidis/tafamidis and placebo/tafamidis).

For Cohort B, descriptive statistics for change from baseline at each post-baseline visit will be provided for NT-proBNP and Troponin I.

6.3. Subset Analyses

All Cohort A and Cohort B analyses will be repeated by genotype (wild type and variant) separately.

6.4. Baseline and Other Summaries and Analyses

Subjects disposition, demographics, treatment exposure, and concomitant medications will be summarized descriptively for both Cohort A and Cohort B separately.

6.5. Safety Summaries (including other endpoints)

All safety endpoints listed in this section will be analyzed descriptively for Cohorts A and B separately.

6.5.1. Adverse Events

All AE data collected on the CRF will be presented in summary tables and data listings.

All adverse events that are observed from the time of first dosing with study medication until the treatment end date will be included in the safety analysis. Adverse events that occurred during treatment will be reported separately if the event occurred prior to randomization.

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. Treatment emergence is defined in Section 3.5.1.

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. All subjects in both Cohort A and B will be permitted one open label dose-reduction to 20 mg. All adverse events that led to temporary dose discontinuation or dose reduction will be summarized.

For Cohort A subjects who ended participation in B3461045 study without achieving the completion criteria of sustainable access to tafamidis by prescription, and allowed to return to the study and continue participation until they reach protocol defined study completion, adverse events that occurred between the time a subject ended the participation and subsequently returned will be collected and evaluated for treatment-emergence in the same manner as adverse events that occurred during the study participation.

Given that in B3461045 all subjects will be receiving active treatment, 3-tier analysis will not be performed on the adverse events.

6.5.2. Laboratory Data

All clinical laboratory data (serum chemistry, coagulation, hematology, and urinalysis) will be subjected to clinical review and summarized by frequency of events and mean changes from baseline.

There was a Quality Event investigation (PR 2163545) concerning repeated data for the assessment of respiratory rate and urine dipstick at site 1121. The investigation could not confirm whether the repeated data was fraudulent or due to human error. To evaluate the impact of these findings on the overall interpretation of the endpoints potentially impacted, the laboratory analyses specified above will be repeated by excluding all subject data from this site 1121. Overall results will be compared to summaries generated by excluding the site to assess if there was a meaningful impact on the clinical interpretation.

6.5.3. Electrocardiogram

ECG values at each visit and change from baseline will be presented in summary tables and data listings. Descriptive statistics will be provided for each test result by visit.

Centrally over-read ECG variables will be summarized by mean change from baseline to end of study for heart rate, PR interval, QRS width, QT interval, and QTcB (Bazett's correction) and QTcF (Fridericia's correction) values. Additionally, the incidence of categorical increases in QTc intervals will be provided. Categories for QTcB and QTcF are ≥450 msec, ≥480 msec, and ≥500 msec. Categories for QTcB and QTcF 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 anticipated to be more appropriate.

6.5.4. Physical Examinations and Vital Signs

Physical examinations and vital signs (lying and standing blood pressure and pulse, respiratory rate, and temperature) will be summarized using descriptive statistics.

To assess the impact of the findings in the Quality Event investigation described in Section 6.5.2, vital signs summaries will also be generated by excluding all subject data from site 1121. Overall results of vital signs will be compared to summaries generated by excluding the site to assess if there was a meaningful impact on the clinical interpretation.

7. INTERIM ANALYSES

7.1. Introduction

Interim analyses may be performed if required to meet regulatory requirements and as requested by the Data Monitoring Committee. Interim analyses may also be performed during the course of the study to allow for the reporting of data to the scientific community.

7.2. Interim Analyses and Summaries

Interim analyses will include either all the analyses or a subset of the summaries described in Sections 5 and 6.

8. REFERENCES

Not Applicable.

9. APPENDICES

Appendix 1. SUMMARY OF ANALYSES

Summary of Proposed Analyses

End Point or Assessment	Overall ##	Wild-type vs Variant
All cause mortality.#	x	x
Cardiovascular related mortality.#	x	x
Frequency of all cause hospitalization.	x	x
Frequency of cardiovascular related hospitalization (including heart failure, arrhythmia, myocardial infarction, stroke and other cardiovascular related events).	x	x
Change from baseline at each visit in Kansas City Cardiomyopathy Questionnaire Overall Score, domain scores (Physical limitation, Symptom stability, Symptom frequency, Symptom burden, Total symptom, Self efficacy, Social limitation, and Quality of life) and clinical summary score #	x	x
New York Heart Association classification at each visit.	x	x
Change from baseline in Body Mass Index/modified Body Mass Index at each visit.	x	x
Change from baseline in NT-proBNP at each visit.#	x	x
Change from baseline in Troponin I at each visit.#	x	x
Assessment of physical examinations, use of concomitant medications, electrocardiograms (ECGs), clinical laboratory testing, vital signs at each visit.	x	x

Cohort A Analysis will include data from B3461028.

Overall implies that it is not subgroup analysis. For Cohort A, summaries are provided by "Tafamidis/Tafamidis" and "Placebo/Tafamidis" groups. For Cohort B, summaries are provided by "Tafamidis" group.

Appendix 1.1. Definition and Use of Visit Windows in Reporting

For the purpose of this study, Day 1 is defined as the first dose day under this protocol (except for mortality-based endpoints,KCCQ, NT-proBNP, and Troponin I).

The following describes the clinical visit windows allowed within the protocol:

Clinic Visits (Months 6, 12, 18, 24, 30, 36, 42, 48, 54) ±2 weeks

End of Study Visit (Month 60) ±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:

Clinic Visits (Months 6, 12, 18, 24, 30, 36, 42, 48, 54) ±3 months

All nominal visits (months 6, 12, 18, 24, 30, 36, 42, 48, 54) 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.

Data from endpoints that are collected at “Month 3” either in France or Germany as part of the country-specific protocol amendment will be summarized descriptively as ‘Month 3- Unscheduled’ and will not be subject to the windowing rules described above.

Analyses of KCCQ, NT-proBNP, Troponin I will combine data from B3461028 study. For these endpoints, visits for B3461045 will be evaluated as “30 Months” plus the visit window calculated using the B3461045 windowing rules specified above.

Appendix 2. STATISTICAL METHODOLOGY DETAILS

Sample SAS code for time to event analysis 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 to fit the mixed model repeated measures 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;
```