Protocol B3461023

OPEN-LABEL SAFETY AND EFFICACY EVALUATION OF FX-1006A IN SUBJECTS WITH TRANSTHYRETIN (TTR) AMYLOIDOSIS

Statistical Analysis Plan
(SAP)

Version: **2**

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Date: Sep 11, 2014

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APPENDICES

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

Version 2 is amended from version 1 to include the following:

Change	Date	Section(s) Affected	Corresponds to a Protocol Amendment	Statistician
1. Additional clarification of visit windowing	May 29, 2014	Appendix 1.5	No	PPD
2. An appendix describing how to combine the two forms of data collected describing the subject's ambulatory status and analyses has been added. The treatment of missing data has also been expanded for the ambulatory status data.	May 29, 2014	Appendix 1.8	No	PPD
3. Additional details around the analyses of ambulatory status, including removing the Cox Regression.	Sep 11, 2014	8.1.3 Appendix 1.8	No	PPD
4. Additional details about the analysis of the NIS Total and NIS-UL scores were added for the non-V30M population. Details were added for the MMRM model in the case it doesn't converge.	May 29, 2014	6.1 8.1.1	No	PPD
5. Additional details around the scoring of the NIS and the Norfolk TQoL-DN, including the treatment of missing data for the Norfolk TQoL-DN.	May 29, 2014	Appendix 1.1 Appendix 1.2	No	PPD
6. The LOCF analysis has been removed, due to the nature of the				

discontinuation criteria from this study LOCF is not an appropriate analysis.	May 29, 2014	8.1.1	No	PPD
7. The list of the laboratory measures to be summarized was shortened to those laboratory measures which are potentially related to disease. All values will be listed in the subject listings.	May 29, 2014	6.2.1	No	PPD
8. An Appendix was added describing the summary and handling of the post transplant data. Additionally, the transplant category has been expanded to include heart transplant.	May 29, 2014	Appendix 2	No	PPD
9. Additional details on the definition of orthostatic hypotension were added. An additional summary table was added for treatment emergent orthostatic hypotension.	May 29, 2014	8.3	No	PPD
10. Added formulae for calculating QTc correction factors (QT_{cB} and QT_{cF})	May 29, 2014	Appendix 1.4	No	PPD
11. Removed TTR mutation as a covariate and stated that the analyses will be separate for V30M and non-V30M	May 29, 2014	6.5	No	PPD
12. Added analysis of time to death	July 29, 2014	6.2.5	No	PPD
13. Modified ambulatory status mapping algorithm by assigning subjects who required brace assistance to normal category	July 29, 2014	Appendix 1.8	No	PPD
14. Updated algorithm for imputing missing last dose date of study drug.	July 29, 2014	Appendix 1.6	No	PPD

2. INTRODUCTION

This current study is being conducted to obtain additional safety and efficacy data and to provide continued dosing of tafamidis for up to 10 years, or until subject has access to tafamidis for TTR-FAP via prescription, to patients with TTR-FAP who have not undergone liver or heart transplantation and who have completed either Protocol Fx-006 (EudraCT 2008-001262-87) or Protocol Fx1A-201 (EudraCT 2007-006791-12). Upon regulatory approval for the treatment of TTR-FAP in their respective country and access to prescription tafamidis, subjects may be withdrawn from the study. The decision to withdraw subjects in a country will be done in consultation between the investigator and the sponsor. Subjects will continue to receive once-daily 20 mg tafamidis. Safety will be assessed via the incidence of treatment-emergent AEs, the use of concomitant medications, and by results from clinical laboratory testing, physical examinations, ECGs, and vital signs.

Prior to enrollment in this current study, subjects who complete Protocol Fx-006 will have received study medication for a total of 30 months (18 months of double-blinded treatment in Protocol Fx-005 plus 12 months of open-label treatment in Protocol Fx-006); subjects who complete Protocol Fx1A-201 will have received open-label tafamidis for 12 months.

2.1. Study Design

This is a Phase 3, open-label study designed to obtain additional long-term safety and efficacy data for once-daily tafamidis (20 mg soft gel capsule). In addition, this study will continue to provide subjects with tafamidis who have completed either Protocol Fx-006 (a 1-year, open-label extension study to Protocol Fx-005 which is a randomized, double-blind, placebo-controlled, 18-month study to evaluate the safety and efficacy of tafamidis) or Protocol Fx1A-201 (a Phase 2, open-label study to evaluate TTR stabilization, safety and tolerability of tafamidis) for up to 10 years or until subject has access to tafamidis for TTR-FAP via prescription. Upon regulatory approval for the treatment of TTR-FAP in their respective country and access to prescription tafamidis, subjects may be withdrawn from the study. Such subjects will be considered study completers. The decision to withdraw subjects in a country will be done in consultation between the investigator and the sponsor. Any subject who is determined during this study to have developed severe chronic renal impairment (creatinine clearance <30 mL/minute as determined by the Investigator) will be asked to participate in a renal sub-study. CCI [redacted]

2.2. Study Objectives

- *To obtain additional, long-term, open-label safety and efficacy data for tafamidis (Fx-1006A) in subjects with TTR-FAP.*

- *To continue to provide the investigational product tafamidis (Fx-1006A) to subjects with TTR-FAP who have completed Protocol Fx-006 or Protocol Fx1A-201.*

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

Given the lack of long-term data in TTR-FAP, interim analyses will be performed during the course of the study to allow for the reporting of safety and efficacy data to the scientific community through presentation at scientific and professional meetings or for regulatory purposes. Analyses can also be performed for publication of safety and efficacy data provided there is Pfizer cross functional line review and agreement.

This is an open-label study as such the data will not need to be unblinded.

Final analyses will be performed after database release.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

This study is descriptive in nature, and as such, there are no formal hypotheses to be tested.

4.2. Statistical Decision Rules

The data will be summarized using descriptive measures with 95% confidence intervals. Additionally, the data will be presented by treatment group (from the Fx-005 randomization) and TTR mutation. The two treatment groups will be referred to as Tafamidis-Tafamidis and Placebo-Tafamidis based on the original randomization to Tafamidis and Placebo in Fx-005.

5. ANALYSIS SETS

5.1. Intention to Treat (ITT) Population

The intent to treat (ITT) population consists of all subjects who are enrolled in this study, who have taken at least one dose of study medication, and who have baseline and at least one post-baseline NIS-LL measure. This population will be used for efficacy analysis.

5.2. Safety Analysis Population

The safety analysis population consists of all subjects who are enrolled in this study and who have taken at least one dose of study medication.

Per the protocol, *subjects undergoing liver and/or heart transplantation while participating in this study will no longer receive investigational product. However, subjects who do undergo a liver transplant will not be withdrawn from this study and will be asked to return to the clinical unit post-transplantation on an annual basis for NIS, Norfolk QOL-DN, and Karnofsky Performance Scale Index evaluations, safety assessments, and to assess subject ambulation.* If a subject has had a liver transplant and remains in the study, that subject's data will be omitted for all post-transplant visits from the summary analyses in the ITT and safety populations.

5.3. Liver and/or Heart Transplant Subjects

Data for subjects who have received a liver transplant during the course of this study and who remain in the study will have their post-transplant data summarized separately. Appendix 2 will describe the summary table and listings to be produced.

5.4. Protocol Deviations

In order to closely mimic actual drug behavior in medical practice, no protocol deviation will exclude a subject from the summaries for either the ITT or safety populations.

6. ENDPOINTS AND COVARIATES

6.1. Efficacy Endpoint(s)

- The Neuropathy Impairment Score (NIS): the following subscales from the NIS will be summarized: (NIS-LL, NIS-LL-MW, NIS-LL-Reflexes, NIS-LL Sensory, NIS-LL scores for: toe, ankle, knee and hip);
  Due to the fact that the full NIS was not collected in the parent studies, the NIS Total Score and NIS-UL will not be summarized for the V30M population, since there is no pre-study baseline. However, the NIS Total Score and NIS-UL will be summarized for the non-V30M population.
- The Total Quality of Life (TQOL) score as measured using the Norfolk Quality of Life for diabetic neuropathy (QOL-DN) questionnaire (including the following subscales: Total QOL, Physical Functioning/Large Fiber, Activities of Daily Living (ADLs), Symptoms, Small Fiber, Autonomic);
- The Karnofsky Performance Scale Index;
- BMI and mBMI;
- Assessment of subject ambulation.

6.2. Safety Endpoints

6.2.1. Clinical Laboratory Endpoints

The following list of clinical laboratory endpoints was collected during the course of the study. However, the summary tables will be restricted to the measures indicated with an asterisk (*). All measures will be included in the subject listings.

6.2.1.1. Serum chemistry

a. Sodium
b. Globulin
c. Potassium
d. Alkaline phosphatase (ALP)*
e. Alanine aminotransferase (ALT)*
f. Chloride
g. Aspartate aminotransferase (AST)*

h. Bicarbonate
i. Blood urea nitrogen*
j. Gamma glutamyl transferase*
k. Creatinine*
l. Cholesterol
m. Calcium
n. Uric acid
o. Inorganic Phosphorous
p. Thyroid-stimulating hormone*
q. Glucose *
r. Total thyroxine (T4)*
s. Total bilirubin*
t. Free T4*
u. Total proteins
v. Prealbumin (transthyretin)*
w. Albumin*
x. Retinol-binding protein
y. NT-pro-BNP*
z. Troponin I*
aa. Troponin T*

6.2.1.2. Coagulation

a. Prothrombin time*
b. INR*

6.2.1.3. Hematology

a. Hemoglobin
b. Platelets
c. Hematocrit
d. White blood cell count*
e. Red blood cell count
f. Neutrophils*
g. Lymphocytes*
h. Mean corpuscular volume
i. Monocytes*
j. Mean corpuscular hemoglobin
k. Eosinophils*
l. Mean corpuscular hemoglobin concentration
m. Basophils*

6.2.2. Urinalysis

a. pH
b. Blood (free Hb)

c. Protein
d. Nitrite
e. Glucose
f. Urobilinogen
g. Ketones
h. Specific gravity
i. Bilirubin

6.2.3. Physical exam and Medical history

Physical exam will be listed by subject and visit in the listings. Medical history will be listed by subject.

6.2.4. ECG

ECG data will be summarized at each visit. A summary of ECG abnormalities will be presented, including changes from normal to abnormal or abnormal to normal. In addition, a summary of the number of subjects who meet the following criteria for QTc, using both the Bazett's and Frederica correction factors, will be presented:

- a change from baseline $\geq$ 60 msec,
- a change from baseline $\geq$ 90 msec;
- a change from baseline between 30 msec (inclusive) and < 60 msec;
- a reading of greater than 450 msec at any visit;
- a reading of greater than 480 msec at any visit;
- a reading of greater than 500 msec at any visit.

6.2.5. Death

Time to death will be calcuated from the first dose of the treatment (either Fx-005 or Fx1A-201), from active treatment start, and from onset of symptom, respectively. Subjects alive at the end of the study will be censored at the last visit date. For subjects who have received a liver and/or heart transplant, time will be censored at the time of transplant. Death after discontinuation will be censored at time of discontinuation. The date of onset of symptom is the start date of the earliest symptom related to ATTR in the Medical History CRF.

6.3. Adverse Events

Treatment emergent adverse events will be summarized by all causes and treatment relatedness groupings. For the purposes of this study, treatment emergent is defined as an event which begins after enrollment in the current study (B3461023) or which worsens during the course of the current study. In addition, severity of the adverse events will be summarized by all causes and treatment relatedness.

6.4. Discontinuations

All reasons for discontinuation will be summarized including: discontinuations due to adverse events, discontinuations due to laboratory abnormalities, discontinuations due to

death, discontinuations due to liver and/or heart transplant, discontinuations due to other causes (not laboratory abnormalities, death or liver transplant), and all cause discontinuation.

6.5. Covariates

Due to the small number of subjects and the descriptive nature of this study, baseline will be used as a covariate in the change from baseline models and where appropriate, gender. TTR mutations will be categorized as V30M or nonV30M and all analyses will be done separately by these TTR mutation groupings.

6.6. Baseline

The baseline for all measures will be the last measurement prior to the first dose of study drug in study Fx-005 or Fx1A-201. For the V30M subjects, an additional set of analyses will be performed using a second baseline, the last measurement prior to active treatment from study Fx-005 or Fx-006.

7. HANDLING OF MISSING VALUES

Data based on entire scales which are missing will be analyzed as follows:

If the data are time until event data and there is no observed event (at any point during the trial) the observation will be censored at the last observation. If there was an observed event, the data associated with the first observation of that event will be used, all other observations will not be needed.

For all change from baseline analyses, the data will be analyzed as follows: for analyses at each visit, the missing observations will not be used as the models will be estimated using an Mixed Model Repeated Measure (MMRM) model for the analysis.

7.1. Norfolk Quality of Life – Diabetic Neuropathy (QoL-DN)

If missing responses to questions occur, missing scores will be imputed as the mean of the non-missing questions within the domain for that visit as long as at least 60% of the items within the domain have a non-missing response. The domain score will then be the sum of the non-missing and imputed questions. If all 35 questions are non-missing or imputed as defined above, then the TQOL will be calculated as the sum of the non-missing items and the imputed values. If questions could not be imputed as defined above due to less than 60% of responses in a domain; however, at least 60% of the total questions are either non-missing or imputed, then the TQOL will be calculated as the mean of the non-missing and imputed questions times 35. If greater than 40% of the items in a domain or TQOL are missing, then the domain is deemed missing.

7.2. Neuropathic Impairment Score (NIS)

If any question is answered as ‘N/A’ then the score for that question will be 0. Additional missing imputation rules are provided in Appendix 1.1.

7.3. The Karnofsky Performance Scale Index

The Karnofsky Performance Scale Index is a single item scale, and, as such; missing values will be excluded from analyses.

7.4. Assessment of Subject Ambulation

If the first available assessment indicates no impairment of ambulation, then all previous missing assessments will be set to no impairment of ambulation. However, if the first available assessment indicates any level of impairment then all previous missing assessments will remain as missing.

If an assessment is missing but there are assessments surrounding the missing assessment and the assessments surrounding the missing assessment are the same, the missing assessment will be set to that value. If the assessment before the missing assessment is different from the assessment after the missing assessment, then the missing assessment will be excluded from the analyses. Missing assessment after the date of change or start of ambulatory status will be set to the value last seen with the change or start of the status.

Changes in ambulatory assessment that are noted as due to circumstances unrelated to disease progression (determined either through investigator determination or clinical definition) will be set to the status last seen for that subject for that visit; an example would be: leg fracture requiring crutches.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

8.1.1. Analyses for Continuous Data

All continuous data will be summarized with descriptive statistics, including mean, standard deviation, median, range and 95% confidence intervals. In addition, change from baseline statistics will be presented as appropriate, to include the appropriate descriptive statistics. For the change from baseline statistics, the estimate will be adjusted for baseline (where appropriate) and the LSMean and standard error will be presented with the 95% confidence interval.

These summaries will be provided by treatment group and by TTR mutation.

For the V30M subjects, a repeated measures analysis of covariance model with change from baseline as the dependent variable, an unstructured covariance matrix, treatment, month and treatment-by-month as fixed effects, baseline as covariate and subject as a random effect in the model will be used to estimate the LSMeans and confidence intervals as indicated above. A sensitivity analysis will also be conducted using the model shown above however, without baseline as a covariate. See Appendix 1.7 for an example of the SAS code for this analysis.

In the event that the model will not converge due to the limited amount of data at the later visits, the model will be evaluated up to the point that it will converge. The data after that

point will be summarized using descriptive statistics only and for the T-T and P-T groups will not be compared and no p value will be produced.

Separate analyses will be conducted using both measurements of baseline, at study start and at active treatment start as specified above. Due to the 18 month length of Fx-005 and the fact that many of the outcomes are measured annually, the measurements aren't at the same time points (for example, 3 years of active treatment); this disparity of treatment schedules will not allow a direct comparison of the subjects' change from baseline on active treatment, at any time point after the parent trials; therefore, just descriptive statistics will be reported for the outcomes measured annually.

For the non V30M subjects, a repeated measures analysis of covariance model with change from baseline as the dependent variable, an unstructured covariance matrix, month as fixed effect, baseline as covariate and subject as a random effect in the model will be used to estimate the LSMeans and confidence intervals. A sensitivity analysis will also be conducted using the model shown above however, without baseline as a covariate.

8.1.2. Analyses for Categorical Data

All categorical data will be summarized as n, percentage and 95% confidence intervals. These summaries will be provided by treatment group and by TTR mutation. Separate analyses will be conducted using both measurements of baseline, at study start and at active treatment start as specified above.

Confidence intervals will be based on estimates of the binomial probabilities with no adjustments to the probabilities.

8.1.3. Analyses for Time to Event Endpoints

Kaplan-Meier estimates will be computed for all time to event endpoints, including median , interquartile ranges, and 95% confidence intervals. Kaplan-Meier curves will be presented at yearly intervals. These analyses will be provided by treatment group and by TTR mutation. Separate analyses will be conducted using both measurements of baseline, at study start and at active treatment start as specified above. Additionally, a set of analyses will be done for the time from onset of symptom.

8.2. Efficacy Analyses

The efficacy endpoints for this study are the cumulative efficacy data as measured by the Neuropathy Impairment Score (NIS); the Total Quality of Life (TQOL) score as measured using the Norfolk Quality of Life for Diabetic Neuropathy (QOL-DN) questionnaire; the Karnofsky Performance Scale Index; and the Modified Polyneuropathy Disability (mPND) score of ambulatory status.

The following measures will be analyzed using the methods described above for continuous outcomes in Section 8.1.1: NIS-LL, TQOL, Karnofsky Performance Scale Index. These analyses will be provided by treatment group and by TTR mutation.

The assessment of subject ambulation will be analyzed using the methods described above for categorical measures in Section 8.1.2. Due to the fact that there are two substantially different versions of the CRF page, the data will be summarized three ways: for the original CRF, for the revised CRF and for the combined recoded data. In addition, shift tables will be presented showing the distribution of subjects with a change in ambulation based on the combined recoded data. Finally, if there are sufficient numbers of subjects who demonstrate a change in ambulation stage, , then Kaplan-Meier estimates will be computed for the time to the next ambulatory stage (see details in Appendix 1.8). These analyses will be provided by treatment group and by TTR mutation.

8.3. Safety Analyses

Safety data will be summarized for the safety analysis population.

Treatment and Disposition of Subjects: Subject evaluation groups will show end of study subject disposition and will show which subjects were analyzed for efficacy, as well as for safety (adverse events and laboratory data). Frequency counts will be supplied for subject discontinuation(s) by treatment.

A listing of treatment duration for each subject will be reported in accordance with the sponsor reporting standards.

Demographic and Baseline Characteristics. A break-down of demographic data will be provided for age, gender, race, weight, body mass index, and height. Each will be summarized by treatment group, sex at birth and 'All Subjects' in accordance with the sponsor reporting standards. All baseline and disease characteristics will also be summarized.

Discontinuations. Subject discontinuations due to adverse events will be detailed and summarized.

Adverse events (AEs): Treatment emergent adverse events will be summarized by causality and severity.

Hematology, Biochemistry and Urinalysis: Descriptive statistics will be provided for each test result and for change from baseline by visit. Additional summaries for abnormalities in laboratory measures will be provided for the following populations: without regard to baseline, abnormal at baseline and normal at baseline.

Baseline is defined in two ways as described above.

ECG: Changes from baseline (defined as the last evaluation prior to the first dose of study drug) will be summarized for each of the ECG measures listed above. In addition, ECG changes from baseline will be categorized as follows:

- a change from baseline ≥ 60 msec,
- a change from baseline ≥ 90 msec;
- a change from baseline between 30 msec (inclusive) and < 60 msec;
- a reading of greater than 450 msec at any visit;
- a reading of greater than 480 msec at any visit;
- a reading of greater than 500 msec at any visit.

Baseline is defined in two ways as described above.

Note: In Italy only Echocardiograms and Holter Monitoring were performed, and therefore, the Italian subjects will not be included in these summaries.

Vital signs: Will be summarized using descriptive statistics, to include: values at each visit, change from baseline to each visit and a categorization of clinically significant changes. A summary table of subjects experiencing orthostatic hypotension at each visit will be included. A table summarizing the subjects who experienced treatment emergent hypotension will be created.

Baseline is defined in two ways as described above.

Significant changes from baseline are defined as follows:

- Systolic Blood Pressure (mmHg) Decrease (Change ≤ -20, or Value < 90)
- Systolic Blood Pressure (mmHg) Increase (Change ≥ 20, or Value > 180)
- Diastolic Blood Pressure (mmHg) Decrease (Change ≤ -15, or Value < 50)
- Diastolic Blood Pressure (mmHg) Increase (Change ≥ 15, or Value > 105)
- Heart Rate (bpm) Decrease (Change ≤ -15, or Value < 50)
- Heart Rate (bpm) Increase (Change ≥ 15, or Value > 120)
- Weight (kg) Decrease (Change ≤ -7%)
- Weight (kg) Increase (Change ≥ 7%)

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Concomitant medications: will be summarized.

Physical Examination: Results will be listed.

9. LIST OF TABLES

The List of Tables will be provided in a separate addendum.

10. LIST OF LISTINGS

The List of Listings will be provided in a separate addendum.

11. LIST OF FIGURES

The List of Figures will be provided in a separate addendum.

12. APPENDICES

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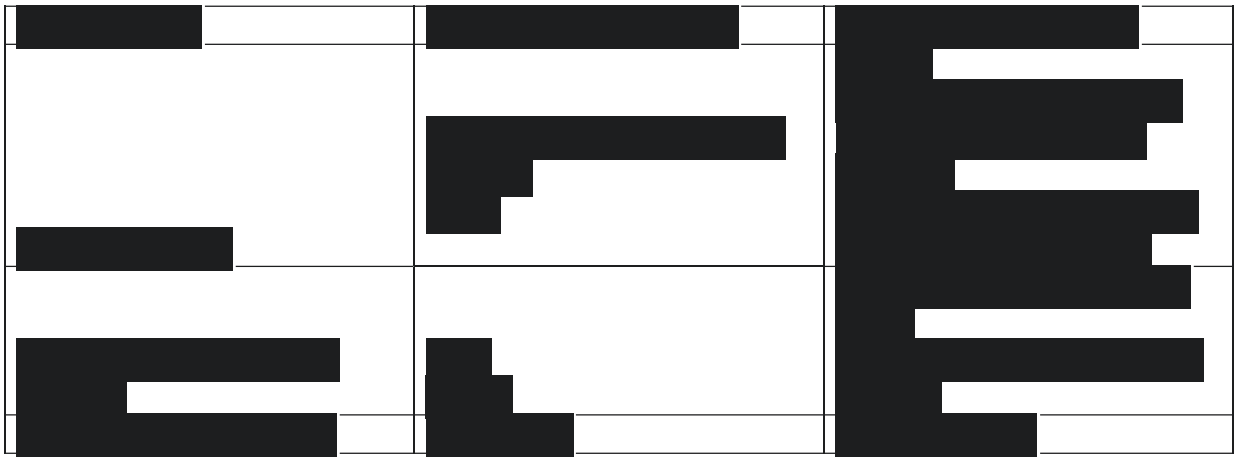

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