Protocol Fx1B-303 (B3461026)

Open-Label Safety and Efficacy Evaluation of Fx-1006A

in Subjects with V122I or Wild-Type

Transthyretin (TTR) Amyloid Cardiomyopathy

Statistical Analysis Plan (SAP)

Version	Date	Author
Original	29May2014	PPD, SCBU Statistics
Amendment 1	04Nov2015	PPD, Manager, GIPB RDRO Group

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

Amendment 1, 31Oct2015: The Statistical Analysis Plan has been amended to include the following:

Change	Date	Section(s) Affected	Corresponds to a Protocol Amendment	Statistician
1. Changed the word patient to subject in order to agree with the amended protocol.	May 29, 2014	Throughout	Yes (# 1)	PPD
2. Additional information on the use of interim analyses.	May 29, 2014	3.2	Yes (# 1)	PPD
3. Additional clarification of visit windowing	May 29, 2014	Appendix 2	No	PPD
4. Additional clarification of missing data rules is included.	May 29, 2014	Appendix 3	No	PPD
5. Clarification of the categorical outcome variable analyses has been included, as well as the addition of shift tables for the analysis of these variables.	May 29, 2014	8.1.2	No	PPD
6. 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. Additionally, duplicated laboratory measures were removed.	May 29, 2014	6.2 item 7	No	PPD
7. The report of physical examinations has been changed from a summary to a listing and a listing of medical history has been added	May 29, 2014	6.3	No	PPD

8. 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	7	No	PPD
9. The specification and summary of the use of pacemakers and/or defibrillators were added.	May 29, 2014, Nov 3, 2015	8.3	No	PPD
10. The cox regression models for time to event were removed due to the single arm study design.	May 29, 2014	8.1.3	No	PPD
11. Time to event analysis has been modified to specify time from randomization and time from onset of disease.	May 29, 2014	8.1.3	No	PPD
12. Added specifications for a table of clinically significant ECGs.	May 29, 2014	8.3	No	PPD
13. Added formulae for calculating QTc correction factors (QT_{cB} and QT_{cF}).	May 29, 2014	Appendix 1.3	No	PPD
14. Replaced the scoring for the KCCQ with a clearer version of the manual to agree with the programming used in Fx1B-201.	May 29, 2014	Appendix 1.1	No	PPD
15. Clarified Section 6.1 and 8.2 for efficacy endpoints and analyses to be consistent with the protocol.	May 29, 2014	6.1 and 8.2	No	PPD
16. Clarification of the data points for the 6 minute walk test Borg scale values.	May 29, 2014	6.1, item, 4c	No	PPD
17. Eliminated an overlap in ECG change	May 29, 2014	6.2, item 6k	No	PPD

categories.				
18. Corrected typographic error. Changed PRS to QRS.	May 29, 2014	6.2, item 6c	No	PPD
19. Added specifications for clinical significant changes in vital signs and definition of orthostatic hypotension.	May 29, 2014	8.3	No	PPD
20. Added analyses of mortality and hospitalization.	Sep 19, 2014	8.3	No	PPD
21. Added delayed entry model for time to mortality analysis from symptom onset.	June 12, 2015	8.1.3 and Appendix 5	No	PPD
22. Added the definitions of cardiac-related death and cardiac-related hospitalizations.	June 12, 2015	6.2	No	PPD

2. INTRODUCTION

This is a Phase 3, open-label study designed to obtain additional, long-term, open-label safety and efficacy data for Tafamidis, and to continue to provide subjects who have completed Protocol Fx1B-201 (a Phase 2, open-label study to evaluate TTR stabilization, as well as the safety and tolerability of Tafamidis) with 20 mg oral Tafamidis (soft gelatin capsule) for ten years or until tafamidis is commercially available for the subjects in this study.

Eligible subjects will continue once-daily dosing with 20 mg Tafamidis at home on Day 1 (i.e., first dose) and will return to the clinical unit for study visits every 6 months, with telephone visits every 3 months between the clinic visits.

2.1. Study Design

This is a Phase 3, open-label study designed to obtain additional, long-term, open-label safety and efficacy data for tafamidis, and to continue to provide subjects who have completed Protocol Fx1B-201 (a Phase 2, open-label study to evaluate TTR stabilization, as well as the safety and tolerability of tafamidis) with 20 mg oral tafamidis (soft gelatin capsule) for up to 10 years or until subject has access to tafamidis for TTR-CM via prescription. Upon regulatory approval for the treatment of TTR-CM 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 to transition to commercial tafamidis will be done in consultation between the investigator and the sponsor).

Subjects who successfully complete Protocol Fx1B-201 will be eligible to enter study Fx1B-303.

2.2. Study Objectives

1 *To obtain additional, long-term, open-label safety and efficacy data for tafamidis in subjects with TTR-CM.*

2 *To continue to provide the investigational product tafamidis to subjects with TTR-CM who have completed Protocol Fx1B-201.*

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

3.1. Data Safety Monitoring Board (DSMB)

The study will be reviewed by an independent DSMB to assess the safety of subjects participating in the protocol on an ongoing basis. The DSMB consists of an independent medical monitor (who also serves as chairperson), two external cardiology experts, and an independent statistician. The DSMB will review cumulative safety data on a periodic timetable. Handling of this data is described in detail in the DSMB Charter. The DSMB can recommend that the study team modify or discontinue the trial due to safety concerns.

3.2. Additional Interim Analyses

Given the lack of long-term data in TTR-CM, 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.

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.

5. ANALYSIS SETS

5.1. 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.

5.2. 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 cardiac measure. This population will be used for efficacy analysis.

6. ENDPOINTS AND COVARIATES

6.1. Efficacy Endpoints

1. Patient Global Assessment: Severity at each visit and change from baseline
2. Patient Global Assessment: Improvement at each visit
3. New York Heart Association (NYHA) Classification: by category and improvement: at each visit
4. 6-Minute walk test: at each visit and change from baseline
    a. Distance walked (in meters)
    b. Categories of distance walked (<300 meters, 300-374.9 meters, 375-449.9 meters, and ≥450 meters)
    c. Pre- and post-baseline dyspnea and fatigue values (using the Borg Scale). This will yield four values for analysis per post-baseline visit. The pre walk test

values, the post walk test values, the within difference value and the change from baseline difference value [that is the difference between the baseline difference value and the visit difference value].

d. Based on the categories defined in b, subjects will be classified as improved, no change or worsened.

5. Kansas City Cardiomyopathy Questionnaire (KCCQ): at each visit and change from baseline
   a. Physical limitations
   b. Self-efficacy
   c. Symptom stability
   d. Quality of life
   e. Symptom frequency
   f. Social limitation
   g. Symptom burden
   h. Overall summary score
   i. Total symptom score
   j. Clinical summary score

6.2. Safety Endpoints

1. Echocardiography: at each visit and change from baseline
   a. Interventricular septal thickness (mm)
   b. Posterior left ventricular wall thickness (mm)
   c. Left atrial diameter (mm)
   d. Left atrial volume (cc)
   e. Left ventricular end diastolic diameter (mm)
   f. Left ventricular mass (g)
   g. Ejection fraction (%)
   h. Right ventricular wall thickness (mm)
2. Doppler data
   a. E/A ratio
   b. Mitral Deceleration time (msec)
3. Tissue Doppler
   a. Septal s', e', a' (cm/sec)
   b. Lateral s', e', a' (cm/sec)
   c. Pericardial effusion (yes/no)
   d. Valvular abnormalities (thickening, regurgitation)
4. Calculated Echo variables will include, but are not limited to:
   a. Relative LV wall thickness (Post wall thickness X 2 divided by LVED)
   b. LA Volume index (LA size/body surface area)
   c. LV mass/voltage ratio (LV mass divided by largest voltage on ECG)
   d. e:e' ratio
5. Select echocardiogram parameters will be categorized as indicated below:
   a. Left ventricular posterior wall thickness ≥ 13 mm
   b. Left ventricular septal thickness ≥ 13 mm

c. Right ventricular thickness ≥ 7 mm
d. E/A ratio ≥ 2
e. E/Eprime Lateral > 15
f. E/Eprime Septal > 15
g. Ejection fraction < 50%
h. E deceleration time ≤ 150 msec
i. Isovolumic relaxation time (IVRT) ≤ 70 msec
j. Any valve thickening
k. Abnormal respiratory variation of inferior vena cava
l. Pericardial effusion

6. ECG values: at each visit and change from baseline
   a. PR interval (msec)
   b. RR interval (msec)
   c. QRS interval (msec)
   d. QT and QTc interval (msec)
   e. heart rate (bpm)
   f. overall interpretation, normal/ abnormal findings and clinical significance
   g. Corrected QTc will be calculated using Bazett's and Fridericia's correction formulas.
   h. QTc > 450 msec
   i. QTc > 480 msec
   j. QTc > 500 msec
   k. Change in QTc between 30 msec (inclusive) and < 60 msec
   l. Change in QTc ≥ 60 msec
   m. Change in QTc ≥ 90 msec

7. Clinical laboratory tests: at each visit and change from baseline

   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.

   Hematology and Biochemistry

   a. Alkaline phosphatase (ALP)*
   b. Alanine aminotransferase (ALT)*
   c. Aspartate aminotransferase (AST)*
   d. amino-terminal B-type natriuretic peptide (NT-pro-BNP)*
   e. Blood urea nitrogen (BUN)
   f. Gamma glutamyl transferase (GGT)*
   g. Creatinine
   h. Total bilirubin*
   i. International normalized ratio (INR)*
   j. Troponin I*
   k. Troponin T*
   l. Prothrombin time*
   m. Sodium
   n. Globulin

o. Potassium
p. Chloride
q. Bicarbonate
r. Cholesterol
s. Calcium
t. Uric acid
u. Inorganic Phosphorous
v. Thyroid-stimulating hormone
w. Glucose
x. Total thyroxine (T4)
y. Free T4
z. Total proteins
aa. Prealbumin (transthyretin)
bb. Hemoglobin
cc. Platelets
dd. Hematocrit
ee. White blood cell count
ff. Red blood cell count
gg. Neutrophils
hh. Lymphocytes
ii. Mean corpuscular volume
jj. Monocytes
kk. Mean corpuscular hemoglobin
ll. Eosinophils
mm. Mean corpuscular hemoglobin concentration
nn. Basophils
oo. Retinol-binding protein

Urinalysis

a. Bilirubin
b. pH
c. Blood (free Hb)
d. Protein
e. Nitrite
f. Glucose
g. Urobilinogen
h. Ketones
i. Specific gravity

8. Mortality and hospitalization (all-cause and cardiac-related)

   All-cause of mortality is defined as any death occurring during the study. Cardiac-related mortality will be any mortality meeting the following MedDRA criterion:1) AE body system (AEBODSYS) = “CARDIAC DISORDERS”, or 2) AE preferred term (AEDECOD) in (CHEST DISCOMFORT, CHEST PAIN, DEATH, CEREBROVASCULAR ACCIDENT, EMBOLIC STROKE, DISEASE

PROGRESSION). Description on the time to mortality analysis can be found in Section 8.1.3.

All cause of hospitalization is defined as any adverse event for which SAE type "3=Hospitalization" in the Adverse Event (AE) CRF. The cardiac-related hospitalization will be any hospitalization meeting the following MedDRA criterion:1) AE body system (AEBODSYS) = "CARDIAC DISORDERS", or 2) AE preferred term (AEDECOD) in (CHEST DISCOMFORT, CHEST PAIN, DEATH, CEREBROVASCULAR ACCIDENT, EMBOLIC STROKE, DISEASE PROGRESSION).

6.3. Physical exam and Medical history

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

6.4. Adverse Events

Treatment emergent adverse events will be summarized by all causes and treatment relatedness groupings. Treatment emergent is defined as either a new adverse event or a worsening of an ongoing adverse event during the course of Study Fx1B-303 (B3461026). In addition, severity of the adverse events will be summarized by all causes and treatment relatedness.

6.5. 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 and all cause discontinuation.

6.6. Covariates

Due to the small number of subjects, lack of comparator group and the descriptive nature of this study, baseline will be used as a covariate in the change from baseline models and where appropriate, duration of disease will be used as a covariate.

6.7. Baseline

Baseline will be defined for Fx1B-201 and B3461026, respectively. The baseline for Fx1B-201 will be defined as the last measurement prior to the first dose of study drug in Study Fx1B-201. The baseline for B3461026 will be defined as the measurement from the end of study visit of Study Fx1B-201, or from the Day 0 visit of Study B3461026, whichever comes later. Baseline for Fx1B-201 and for B3461026 will be summarized.

7. HANDLING OF MISSING VALUES

Data which are 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 other data types, the data will be analyzed as follows: for analyses at each visit, the missing observations will not be used. Any visit after the subject was discontinued will remain as missing data.

For any subject missing a 12-month visit observation from Study Fx1B-201, if the Day 0 visit observation from theFx1B-303 study is reported, the Day 0 visit observation from the Fx1B-303 will be imputed for the12-month visit observation for Study Fx1B-201.

For specific scoring details, see Appendix 1.

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, IQR, range and 95% confidence intervals. In addition, change from baseline statistics will be presented as appropriate, to include the appropriate descriptive statistics. For analysis of change from baseline, baseline data from protocol Fx1B-201 will be used as baseline for these analyses. For the change from baseline statistics, the estimate will be adjusted for baseline and the LSMean and standard error will be presented with the 95% confidence interval based on an MMRM model with a random effect for subject and covariate of baseline.

8.1.2. **Analyses for Categorical Data**

All categorical data will be summarized as n, percentage and 95% confidence intervals. The 95% CI intervals will be estimated using exact methods due to the decreasing sample size. In addition, a shift table will be provided for such variables as the 6 minute walk test, PGA, and NYHA class.

8.1.3. **Analyses for Time to Event Endpoints**

Kaplan-Meier estimates will be computed for all time to event endpoints, including median and interquartile ranges, where appropriate. 95% confidence intervals will be presented at yearly intervals from the start of the investigational drug (baseline of Fx1B-201). Time to event will use randomization and onset of disease as starting points for the calculation of time to event.

Subjects are required to survive to enroll in the parent study (Fx1B-201). Such conditions yield a left-truncated death time distribution from symptom onset. To account for the potential immortal time bias, the time to death from onset of symptom will be analyzed using the delayed entry (left truncation) technique. Survival probabilities will be calculated conditional on subjects having survived until study entry of the parent study (Fx1B-201). SAS codes for the delayed entry (left truncation) technique are provided in Appendix 5.

8.2. Efficacy Analyses

Efficacy analyses will be performed for cumulative efficacy data as measured by Patient Global Assessment (PGA), New York Heart Association (NYHA) classification, Kansas City Cardiomyopathy Questionnaire (KCCQ), 6-minute walk test (6MWT), echocardiograms, and serum levels of troponin I, troponin T, and NT-proBNP.

The analyses will use the methods described above for these continuous outcomes in Section 8.1.1:

- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- 6-minute walk test (6MWT)
- Echocardiograms
- Serum levels of troponin I, troponin T, and NT-proBNP.

The analyses will use the methods described above for these categorical outcomes in Section 8.1.2:

- Patient Global Assessment (PGA)
- New York Heart Association (NYHA) classification
- 6-minute walk test (6MWT) (categorized by level as described below)

Shift tables will be provided for the following variables:

- Patient Global Assessment (PGA)
- New York Heart Association (NYHA) classification
- 6-minute walk test (6MWT) (categorized as stable, improved, worsened)

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, race, weight, body mass index, and height. Each will be summarized by sex at birth and 'All Subjects' in accordance with the sponsor reporting standards. All baseline and disease characteristics will also be summarized for Fx1B-201 and B3461026, respectively.

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

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

Mortality and Hospitalization (all-cause and cardiac-related): Time to all-cause mortality and time to cardiac-related mortality will be calculated from the first dose of the randomized treatment in Study Fx1B-201, and from onset of symptom, respectively. For cardiac-related mortality, subjects who died for reasons other than cardiovascular will be designated as censored at the time of death. Subjects alive at the end of the study will be censored at the last visit date. Death after discontinuation will be censored at time of discontinuation. For subjects who have received a liver and/or heart transplant, time will be censored at the time of transplant. The analyses will use the methods described for time to event endpoints in Section 8.1.3. The analyses will be performed on the safety analysis population (defined in Section 5.1).

The number and percentage of subjects hospitalized (all-cause and cardiac-related) during the study will be summarized descriptively.

Hematology, Biochemistry and Urinalysis: Descriptive statistics will be provided for each test result and for change from baseline by visit.

Baseline is defined as the last evaluation prior to the first dose of study drug in Study Fx1B-201.

Cardiac Measures: Changes from baseline (defined as the last evaluation prior to the first dose of study drug) will be summarized for each of the cardiac parameters listed above by visit. Clinically significant changes in ECG measures (as indicated by the items in Section 6.2, #6, item h through m) at any point during the study will be summarized.

Pacemaker and defibrillator insertion procedures will be identified through a programmatic search of potentially related terms in the clinical database coupled with a manual review by Pfizer Clinical.

The following MedDRA Lower Level Terms (codes) will be applied to the Medical History, Adverse Events, and Investigator Comments to identify potential procedures in the clinical

database: CARDIOVERTER PLACEMENT (10053015), INSERTION OF IMPLANTABLE CARDIOVERTER DEVICE (10052044), CARDIAC PACEMAKER INSERTION (10007598), PACEMAKER INSERTION (CARDIAC) (10033352), DEFIBRILLATOR/PACEMAKER INSERTION (10069072), IMPLANTABLE DEFIBRILLATOR INSERTION (10049442).

The following terms will also be searched to identify potential associated procedures collected in the Investigator Comments CRF: pacemaker, implantable cardiac device, ICD, AICD, cardioversion, cardioverter, defibrillator, ventricular fibrillation, ventricular tachycardia.

Final search criteria and categorization of pacemaker and defibrillator will be based on the results of the clinical review and will be described in the programming plan prior to database finalization.

The number and percentage of subjects with pacemaker or defibrillator insertion procedures (defined above) will be summarized by category and for overall at baseline of Fx1B-201, the number and percentage of subjects who have such devices implanted during the course of Fx1B-201 and during the course of B3461026 (Fx1B-303), respectively.

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.

Significant changes from baseline are defined as follows:

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

Orthostatic hypotension is present under any of the following conditions:

- (Lying Systolic Blood Pressure - Standing Systolic Blood Pressure) >= 20 mmHg, or
- (Lying Diastolic Blood Pressure - Standing Diastolic Blood Pressure) >= 10 mmHg, or
- (Standing Pulse - Lying Pulse) > 20 bpm along with (Standing Pulse or Lying Pulse > 100bpm)

If pulse is missing at any visit, then evaluate orthostatic hypotension using only blood pressure measures.

Concomitant medications: will be summarized.

Physical Examination and Medical History: Results will be summarized and listed.

APPENDICES

Appendix 1. Data Derivation details

Appendix 1.1. KCCQ (See protocol for a copy of the questionnaire)

The Kansas City Cardiomyopathy Questionnaire
Scoring Instructions

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

1. **Physical Limitation**

   - Code responses to each of Questions 1a-f as follows:

     Extremely limited = 1
     Quite a bit limited = 2
     Moderately limited = 3
     Slightly limited = 4
     Not at all limited = 5
     Limited for other reasons or did not do = <*missing value*>

   - If at least three of Questions 1a-f are not missing, then compute

     Physical Limitation Score = 100*[(mean of Questions 1a-f actually answered) – 1]/4

     (see footnote at end of this document for explanation of meaning of "actually answered")

2. **Symptom Stability**

   - Code the response to Question 2 as follows:

     Much worse = 1
     Slightly worse = 2
     Not changed = 3
     Slightly better = 4
     Much better = 5
     I've had no symptoms over the last 2 weeks = 3

   - If Question 2 is not missing, then compute

     Symptom Stability Score = 100*[(Question 2) – 1]/4

3. **Symptom Frequency**

   - Code responses to Questions 3, 5, 7 and 9 as follows:

     Question 3
     Every morning = 1
     3 or more times a week but not every day = 2
     1-2 times a week = 3
     Less than once a week = 4
     Never over the past 2 weeks = 5

3. **Symptom Frequency (cont.)**

Questions 5 and 7
All of the time = 1
Several times a day = 2
At least once a day = 3
3 or more times a week but not every day = 4
1-2 times a week = 5
Less than once a week = 6
Never over the past 2 weeks = 7

Question 9
Every night = 1
3 or more times a week but not every day = 2
1-2 times a week = 3
Less than once a week = 4
Never over the past 2 weeks = 5

- If at least two of Questions 3, 5, 7 and 9 are not missing, then compute:

S3 = [(Question 3) – 1]/4
S5 = [(Question 5) – 1]/6
S7 = [(Question 7) – 1]/6
S9 = [(Question 9) – 1]/4

Symptom Frequency Score = 100*(mean of S3, S5, S7 and S9)

4. **Symptom Burden**

- Code responses to each of Questions 4, 6 and 8 as follows:

Extremely bothersome = 1
Quite a bit bothersome = 2
Moderately bothersome = 3
Slightly bothersome = 4
Not at all bothersome = 5
I've had no swelling/fatigue/shortness of breath = 5

- If at least one of Questions 4, 6 and 8 is not missing, then compute

Symptom Burden Score = 100*[(mean of Questions 4, 6 and 8 actually answered) – 1]/4

5. **Total Symptom Score**

= mean of the following available summary scores:
Symptom Frequency Score
Symptom Burden Score

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[redacted]

6. Self-Efficacy

- Code responses to Questions 10 and 11 as follows:

  Question 10
  Not at all sure = 1
  Not very sure = 2
  Somewhat sure = 3
  Mostly sure = 4
  Completely sure = 5

  Question 11
  Do not understand at all = 1
  Do not understand very well = 2
  Somewhat understand = 3
  Mostly understand = 4
  Completely understand = 5

- If at least one of Questions 10 and 11 is not missing, then compute

  Self-Efficacy Score = 100*[(mean of Questions 10 and 11 actually answered) – 1]/4

7. Quality of Life

- Code responses to Questions 12, 13 and 14 as follows:

  Question 12
  It has extremely limited my enjoyment of life = 1
  It has limited my enjoyment of life quite a bit = 2
  It has moderately limited my enjoyment of life = 3
  It has slightly limited my enjoyment of life = 4
  It has not limited my enjoyment of life at all = 5

  Question 13
  Not at all satisfied = 1
  Mostly dissatisfied = 2
  Somewhat satisfied = 3
  Mostly satisfied = 4
  Completely satisfied = 5

  Question 14
  I felt that way all of the time = 1
  I felt that way most of the time = 2
  I occasionally felt that way = 3
  I rarely felt that way = 4
  I never felt that way = 5

7. Quality of Life (cont.)

- If at least one of Questions 12, 13 and 14 is not missing, then compute

  Quality of Life Score = 100*[(mean of Questions 12, 13 and 14 actually answered) – 1]/4

8. Social Limitation

- Code responses to each of Questions 15a-d as follows:

  Severely limited = 1
  Limited quite a bit = 2
  Moderately limited = 3
  Slightly limited = 4
  Did not limit at all = 5
  Does not apply or did not do for other reasons = <*missing value*>

- If at least two of Questions 15a-d are not missing, then compute

  Social Limitation Score = 100*[(mean of Questions 15a-d actually answered) – 1]/4

9. Overall Summary Score

= mean of the following available summary scores:
Physical Limitation Score
Total Symptom Score
Quality of Life Score
Social Limitation Score

10. Clinical Summary Score

= mean of the following available summary scores:
Physical Limitation Score
Total Symptom Score

Note: references to "**means of questions actually answered**" imply the following.

- If there are *n* questions in a scale, and the subject must answer *m* to score the scale, but the subject answers only *n-i*, where *n-i* >= *m*, calculate the **mean of those questions** as
  (sum of the responses to those *n-i* questions) / (*n-i*)
  not
  (sum of the responses to those *n-i* questions) / *n*

If doing these calculations seems like too much trouble, consider using one of our tools – available at www.cvoutcomes.org:

- SAS or SPSS code
- Excel spreadsheets
- Web data services

Appendix 1.2. 6 Minute Walk Test Categorization

a. Level 1: < 300 m
b. Level 2: 300-374.9 m
c. Level 3: 375-449.9 m
d. Level 4: ≥ 450 m

The categories above represent increasing levels of ability.

To determine if a subject has improved, you would create a new variable/flag which would be based on the subtraction of [category at time 1] – [category at time 2].

e.g.: baseline category – visit 1 category

If this is negative, for example baseline = 2 and visit 1 = 3, thus 2-3 = -1, then the subject would be indicated as improved.

If the subtraction is 0 then the subject is unchanged. And finally, if the subtraction is positive then the subject worsened.

Appendix 1.3. Calculation of QTc Interval Corrections

Fridericia's heart rate correction formula: $QTcF = QT / (RR)^{1/3}$ where RR = 60/HR;
Bazett's heart rate correction formula: $QTcB = QT / (RR)^{1/2}$ where RR = 60/HR;

Appendix 2. 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.

Day 1 ± 1 week
Every other 3 month telephone visits between clinic visits ± 1 week
Clinic visits every 6 months ± 2 weeks
End of study visit ± 2 weeks

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

Day 0: End of study visit from Fx1B-201
Day 1 + 1.5 months
Telephone contact (every 3 months between clinic visits) ± 1.5 months
Clinic visits (every 6 months) ± 3 months
End of study visit (see details below)

In the event that there is a break between the last visit of the parent study (Fx1B-201,) and the first day of dosing in the current study Fx1B-303 (B3461026); then the visit associated with the first day of enrollment in the current study Fx1B-303 (B3461026) will be the baseline visit of this study.

For an early termination visit within study B3461026 (Fx1B-303): The existing windowing rules will be used and as such, the data in the early termination visit should never replace an existing visit. If the visit covered by the windowing rules above is already populated with an existing visit, then the EOS visit should be mapped forward to the next clinic visit.

As an example, the EOS visit occurs at month 68.
If there is no month 66 visit, then the EOS visit becomes the month 66 visit.
If there is a month 66 visit, then the EOS visit becomes the month 78 visit.

For an unscheduled visit:
If possible, the existing windowing rules will be used, but the data should never replace an existing visit. If the visit is already populated, then the unscheduled visit should be mapped forward to the next appropriate visit for that measure if that visit is available.
As an example, the unscheduled visit occurs at month 68 and the data are collected annually.
If there is no month 66 visit, then the unscheduled visit becomes the month 66 visit.
If there is a month 66 visit, but no month 78 visit then the unscheduled visit becomes the month 78 visit.
If there are both month 66 and month 78 visits, then the unscheduled visit is not included in the summary analyses but is included in the listing as unscheduled.

Appendix 3. Algorithm for imputing missing last dosing date of study drug

If the last dosing date is missing and the subject has discontinued from the study, the following method will be used to impute the missing last dosing date.

If the subject discontinues prior to the next expected visit date (last visit plus 90 days) regardless of reason for discontinuation then the last dosing date is the date of discontinuation or death whichever is first .

If the subject discontinues after the next expected visit date (last visit plus 90 days) then the following will be examined. Note that the use of July 1, 2013 in the algorithm reflects the change in capsules dispensed.

If the last visit was a telephone contact and the last visit is prior to or equal to July 1, 2013 then last dosing day = (last visit + 5 months [151 days]) or date of death or date of discontinuation whichever is first.

If the last visit was a telephone contact and the last visit is after to July 1, 2013 then last dosing day = (last visit + 4.5 months [136 days]) or date of death or date of discontinuation whichever is first.

If the last visit was a clinic visit and the last dosing date is prior to or equal to July 1, 2013 then last dosing day = (last visit + 4 months [121 days]) or date of death or date of discontinuation whichever is first.

If the last visit was a clinic visit and the last dosing date is after to July 1, 2013 then last dosing day = (last visit + 3.5 months [106 days]) or date of death or date of discontinuation whichever is first.

If there is a partial date of last dose which is just the year of last dose then use the previous rule. If the partial date is a month and year then the last dosing date = maximum of last date of the partial date month or the result of the rule whichever is first.

Appendix 4. Example SAS code for Delayed Entry Model in Survival Analysis

Delayed entry model in survival analysis:

The total survival time is the length of time specified by the **time** variable. Entry into Study Fx1B-201 is after the amount of time specified by the **los** variable, which is defined from symptom onset to the start of Fx1B-201. The amount of time that the subjects were at risk in this model is **time - los**.

```
proc phreg data=data; /* add the METHOD=PL option in the baseline
statement only when using SAS version 9.2 or higher */
    model time*deathflag(0)= /entry=los;
  baseline out=table survival=S stderr=stderr atrisk=atrisk /method=pl ;
```