Protocol B3461102

A Phase 1, Open-Label, Randomized, Crossover, Single Dose Study to Estimate the Relative Bioavailability of Variant 12.2 mg Tafamidis Free Acid Tablets and Proposed Commercial 12.2 mg Tafamidis Free Acid Tablets Administered Under Fasted Conditions in Healthy Adult Participants

Statistical Analysis Plan (SAP)

Version: 1

Date: 26 Jul 2022

[redacted]

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NOTE: *Italicized* text within this document has been taken verbatim from the Protocol.

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 26 Jul 2022	Original 09 Jun 2022	N/A	N/A

2. INTRODUCTION

A 12.2 milligram (mg) tafamidis free acid tablet is being developed to replace the current commercial 20 mg tafamidis meglumine dosage formulation.

The purpose of the study is to estimate the relative bioavailability of a variant 12.2 mg tafamidis free acid tablet formulation (Test) and the proposed commercial 12.2 mg tafamidis free acid tablet formulation tested in B3461103 (Reference) to inform dissolution specifications.

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study B3461102.

2.1. Modifications to the Analysis Plan Described in the Protocol

None.

2.2. Study Objectives and Endpoints

Objectives	***Endpoints***
Primary:	***Primary:***
• *To estimate the relative bioavailability of variant 12.2 mg tafamidis free acid tablets (Test) and proposed commercial 12.2 mg tafamidis free acid tablets (Reference) in fasted healthy participants.*	• *AUC_{inf} (if data permit, otherwise AUC_{last}) and C_{max} of tafamidis.*
Secondary:	***Secondary:***
• *Not Applicable*	• *Not Applicable*

Objectives	*Endpoints*
CCI [redacted]	[redacted]
[redacted]	[redacted]

2.3. Study Design

This study will be a Phase 1, open-label, randomized, 2-way crossover, single dose study to estimate the relative bioavailability of PF-06291826 (tafamidis) variant 12.2 mg tafamidis free acid tablets and proposed commercial 12.2 mg tafamidis tablets administered under fasted conditions in healthy participants.

A total of 12 participants will be enrolled. Participants withdrawn from the study may be replaced. Each period will be separated by a washout of at least 16 days between administration of study drug. On Day 1 of each period, participants will receive a single dose of one of the two tafamidis formulations according to the study schema provided in Table 2:

Table 2. B3461102 Treatment Sequence Schema

Sequence	*Period 1*	*Period 2*
1 (n=6)	*A*	*B*
2 (n=6)	*B*	*A*

A: 1 x Variant 12.2 mg tafamidis free acid tablet (Test)
B: 1 x Proposed commercial 12.2 mg tafamidis free acid tablet (Reference)

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

The primary endpoints are plasma AUC_{inf} (if data permit, otherwise AUC_{last}) and C_{max} of tafamidis administered as variant 12.2 mg tafamidis free acid tablet (Test) and proposed commercial 12.2 mg tafamidis free acid tablet (Reference), under fasted conditions. Adjusted geometric mean ratios of AUC_{inf}, AUC_{last} and C_{max} will be derived to estimate relative bioavailability.

3.2. Secondary Endpoint

Not applicable.

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Table 3. Plasma Tafamidis Pharmacokinetic Parameters Definitions

Parameter	***Definition***	***Method of Determination***
AUC_{last}	*Area under the concentration-time curve from 0 to time of last measurable concentration*	*Linear/Log trapezoidal method*
*AUC_{inf}**	*Area under the concentration-time curve from time 0 to infinity*	*$AUC_{(0\text{-}tlast)} + (C_{last}*/k_{el})$, where C_{last}* is the estimated plasma concentration at the last quantifiable time point (C_{last}) estimated form the log-linear regression analysis $C_{last}* = C_{last} \times e^{(-kel \times tlast)}$*
CCI		
C_{max}	*Maximum observed concentration*	*Observed directly from data*
CCI		

**if data permit*

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3.4. Baseline Variables

Baseline characteristics will be collected according to the schedule of activities (SoA) as specified in the protocol.

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4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to releasing the database and classifications will be documented per standard operating procedures.

Participant Analysis Set	***Description***
Enrolled	*"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and randomization/assignment to study intervention. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.*
Full analysis set	*Example: All participants randomly assigned to study intervention and who take at least 1 dose of study intervention.*
CCI [redacted]	[redacted]
PK Concentration	*The PK concentration population is defined as all participants who receive at least 1 dose of tafamidis and who have at least 1 measurable concentration of tafamidis.*
PK Parameter	*The PK parameter population is defined as all participants who receive at least 1 dose of tafamidis and who have at least 1 of the PK parameters of interest calculated.*

5. GENERAL METHODOLOGY AND CONVENTIONS

Final analysis will be performed after study participant data set release following last participant last visit.

5.1. Hypotheses and Decision Rules

No statistical hypothesis will be tested in this study.

5.2. General Methods

5.2.1. Analyses for Binary/Categorical Endpoints

For binary or categorical variables, number of participants, numbers and percentages of participants meeting the categorical criteria will be presented in accordance with the Clinical Data Interchange Standards Consortium and Pfizer Standards (CaPS).

5.2.2. Analyses for Continuous Endpoints

For continuous variables, the data will be summarized using the number of participants, mean, median, standard deviation (SD), minimum, and maximum in accordance with the CaPS. For appropriate PK parameters, geometric mean and geometric coefficient of variation (%CV) will also be summarized.

5.3. Methods to Manage Missing Data

5.3.1. Pharmacokinetic Data

Methods to handle missing PK data are described below.

Concentrations Below the Limit of Quantification:

In all data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. (In listings BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification.).

Deviations, Missing Concentrations and Anomalous Values:

In summary tables and plots of median profiles, statistics will be calculated having set concentrations to missing if 1 of the following cases is true:

1. A concentration has been collected as ND (ie, not done) or NS (ie, no sample).

2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

An anomalous concentration value is one that, after verification of bioanalytical validity, is grossly inconsistent with other concentration data from the same individual or from other participants. For example, a BLQ concentration that is between quantifiable values from the same dose is considered as anomalous. Anomalous concentration values may be excluded from PK analysis at the discretion of the PK analyst.

PK Parameters:

Actual PK sampling times will be used in the derivation of PK parameters. If a PK parameter cannot be derived from a participant's concentration data, the parameter will be coded as NC

(ie, not calculated). (Note that NC values will not be generated beyond the day that a participant discontinues).

In summary tables, statistics will not be presented for a particular treatment group if more than 50% of the data are NC. For statistical analyses, PK parameters coded as NC will also be set to missing.

If an individual participant has a known biased estimate of a PK parameter (due for example to dosing error or an unexpected event such as vomiting before all the compound is adequately absorbed from the gastrointestinal tract), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses. For instance, if a participant has a vomiting event post dose that is within a duration of time that is 2-times the derived median T_{max} for the population for the administered treatment, then the pharmacokineticist should consider the exclusion of the PK concentration data collected following the initial vomiting event in that treatment period and the PK parameter data reported for that treatment period from the datasets used to calculate summary statistics or statistical analyses.

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6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

For assessment of the relative bioavailability objective of the study, natural log transformed AUC_{inf}, AUC_{last}, AUC_{72} and C_{max} will be analyzed separately using a mixed effect model with sequence, period and treatment as fixed effects and participant within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios. Treatment A (Variant 12.2 mg tafamidis free acid tablet) will be the Test treatment, while Treatment B (proposed commercial 12.2 mg tafamidis free acid tablet) will be the Reference treatment.

Residuals from the models will be examined for normality and the presence of outliers via visual inspection of plots of residuals vs predicted values and normal probability plots of residuals but these will not be included in the CSR. If there are major deviations from normality or outliers then the effect of these on the conclusions will be investigated through alternative transformations and/or analyses excluding outliers. Justification for any alternative to the planned analysis will be given in the report of the study.

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Table 4. PK Parameters to be Summarized Descriptively by Treatment

Parameter	Summary Statistics
AUC_{inf}, AUC_{last}, CCI, C_{max}	N, arithmetic mean, median, SD, %CV, minimum, maximum, geometric mean and geometric %CV
CCI	[redacted]
[redacted]	[redacted]

For AUC_{inf}, AUC_{last}, and C_{max}, individual participant parameters will be plotted against treatment. Box and whisker plots for AUC_{inf} (if data permits), AUC_{last}, CCI, and C_{max}, will be plotted by treatment.

CCI [redacted]

6.3. Subset Analyses

There are no planned subset analyses.

6.4. Baseline and Other Summaries and Analyses

6.4.1. Baseline Summaries

Demographic and baseline characteristics (age, gender, ethnicity, race, weight, height and body mass index) will be summarized for enrolled population in accordance with the CaPS.

6.4.2. Study Conduct and Participant Disposition

Participants evaluation groups will show end of study participant disposition. Frequency counts will be supplied for participant discontinuation(s) by treatment. Data will be reported in accordance with the CaPS.

6.4.3. Study Treatment Exposure

Study treatment exposure will be listed.

6.4.4. Concomitant Medications and Nondrug Treatments

All concomitant medication(s) as well as non-drug treatment(s) will be reported in the listings.

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7. INTERIM ANALYSES

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating PK modeling, and/or supporting clinical development.

Final analysis will follow the official database release. As this will be an open-label study, there is no formal unblinding of the randomization code.

APPENDICES

Appendix 1. SAS Code for Analysis

An example of the PROC MIXED code is provided below:

For primary objective: Treatment A (Test) vs Treatment B (Reference)

```
proc mixed data=tab.pk;
        class seq period trt participant;
        model l&var=seq period trt/ ddfm=KR;
        random participant(seq) / participant=participant(seq);
        lsmeans trt;
        estimate 'A vs B' trt 1 -1  / cl alpha=0.1;

        ods 'Estimates' out=est&var;
        ods 'lsmeans' out=ls&var;
        ods 'covparms' out=cov&var;
        ods 'tests3' out=tst&var;
run;

/* Letter assignments for treatments (trt) within the estimate statement above are as follows
A: Variant 12.2 mg tafamidis free acid tablet (Test)
B: Proposed commercial 12.2 mg tafamidis free acid tablet (Reference)      */
```

Appendix 2. List of Abbreviations

Abbreviation	Term
%CV	coefficient of variation
AE	adverse event
CCI	[redacted]
AUC_{inf}	area under the concentration-time curve from time 0 to infinity
AUC_{last}	area under the concentration-time curve from 0 to time of last measurable concentration
BLQ	below the limit of quantitation
BP	blood pressure
CaPS	Clinical Data Interchange Standards Consortium and Pfizer Standards
CI	confidence interval
C_{last}	estimated plasma concentration at the last quantifiable time point estimated form the log-linear regression analysis
C_{max}	maximum observed plasma concentration
CSR	clinical study report
ECG	electrocardiogram
HR	heart rate
k_{el}	the terminal phase rate constant calculated by a linear regression of the loglinear concentration-time curve
LLQ	lower limit of quantitation
mg	milligram
N/A	not applicable
NC	not calculated
ND	not done
NS	no sample
PK	pharmacokinetic(s)
PR	pulse rate
QRS	Combination of Q-, R- and S- wave on an electrocardiogram representing ventricular depolarization
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
RR	respiratory rate
SAP	statistical analysis plan
SD	standard deviation
SoA	schedule of activities
CCI	[redacted]
TEAE	treatment emergent adverse event
t_{last}	time of last measurable concentration
CCI	[redacted]