Protocol B3461103

A Phase 1, Open-Label, Randomized, Crossover, Single Dose Study to Determine the Bioequivalence of 12.2 mg Tafamidis Free Acid Tablets and Commercial 20 mg Tafamidis Meglumine Capsules Administered Under Fasted Conditions and the Effect of Food on Oral Bioavailability of 12.2 mg Tafamidis Free Acid Tablets in Healthy Adult Participants

Statistical Analysis Plan
(SAP)

Version: 1

Date: 07 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 07 Jul 2022	Original 19 May 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 determine if a 12.2 mg tafamidis free acid tablet (Test) formulation is bioequivalent to the commercial 20 mg tafamidis meglumine soft gelatin capsule (Reference) and to estimate the effect of food on the bioavailability of the 12.2 mg tafamidis free acid tablet.

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study B3461103.

2.1. Modifications to the Analysis Plan Described in the Protocol

None.

2.2. Study Objectives and Endpoints

Objectives	*Endpoints*
Primary:	***Primary:***
• *To establish the bioequivalence of 12.2 mg tafamidis free acid tablet (Test) and commercial 20 mg tafamidis meglumine soft gelatin capsules (Reference) in fasted healthy participants.*	• *AUC_{inf} (if data permit, otherwise AUC_{last}) and C_{max} of tafamidis.*
Secondary:	***Secondary:***
• *To estimate the relative bioavailability of a single dose of the 12.2 mg tafamidis free acid tablet administered under fed conditions compared to a single dose of the 12.2 mg tafamidis free acid tablet administered under fasted conditions in healthy participants.*	• *Not Applicable*
CCI [redacted]	[redacted]
[redacted]	[redacted]

2.3. Study Design

This study will be a Phase 1, open label, randomized, 3-way crossover, single dose study to determine the bioequivalence of PF-06291826 (tafamidis) 12.2 mg tafamidis free acid tablets versus commercial 20 mg tafamidis meglumine capsules administered under fasted conditions and to estimate the effect of food on the 12.2 mg tafamidis free acid tablet in healthy participants.

A total of 22 participants will be enrolled to ensure a minimum of 18 completers. 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. Participants will be randomized to receive one of the treatment sequences shown in Table 2:

Table 2. B3461103 Treatment Sequence Schema

Sequence	*Period 1*	*Period 2*	*Period 3*
1 (n=11)	*A*	*B*	*C*
2 (n=11)	*B*	*A*	*C*

A: 12.2 mg tafamidis free acid tablet, fasted (Test)
B: Commercial 20 mg tafamidis meglumine soft gelatin capsule, fasted (Reference)
C: 12.2 mg tafamidis free acid tablet, fed (Test)

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 12.2 mg tafamidis free acid tablet and commercial 20 mg tafamidis meglumine soft gelatin capsules, under fasted conditions. Adjusted geometric mean ratios of AUC_{inf}, AUC_{last} and C_{max} will be derived to establish bioequivalence.

In addition, adjusted geometric mean ratios of AUC_{inf}, AUC_{last} and C_{max} of tafamidis administered as 12.2 mg tafamidis free acid tablet under fed conditions, relative to PK prameters under fasted conditions will be derived to estimate the relative bioavailability.

3.2. Secondary Endpoint

Not applicable.

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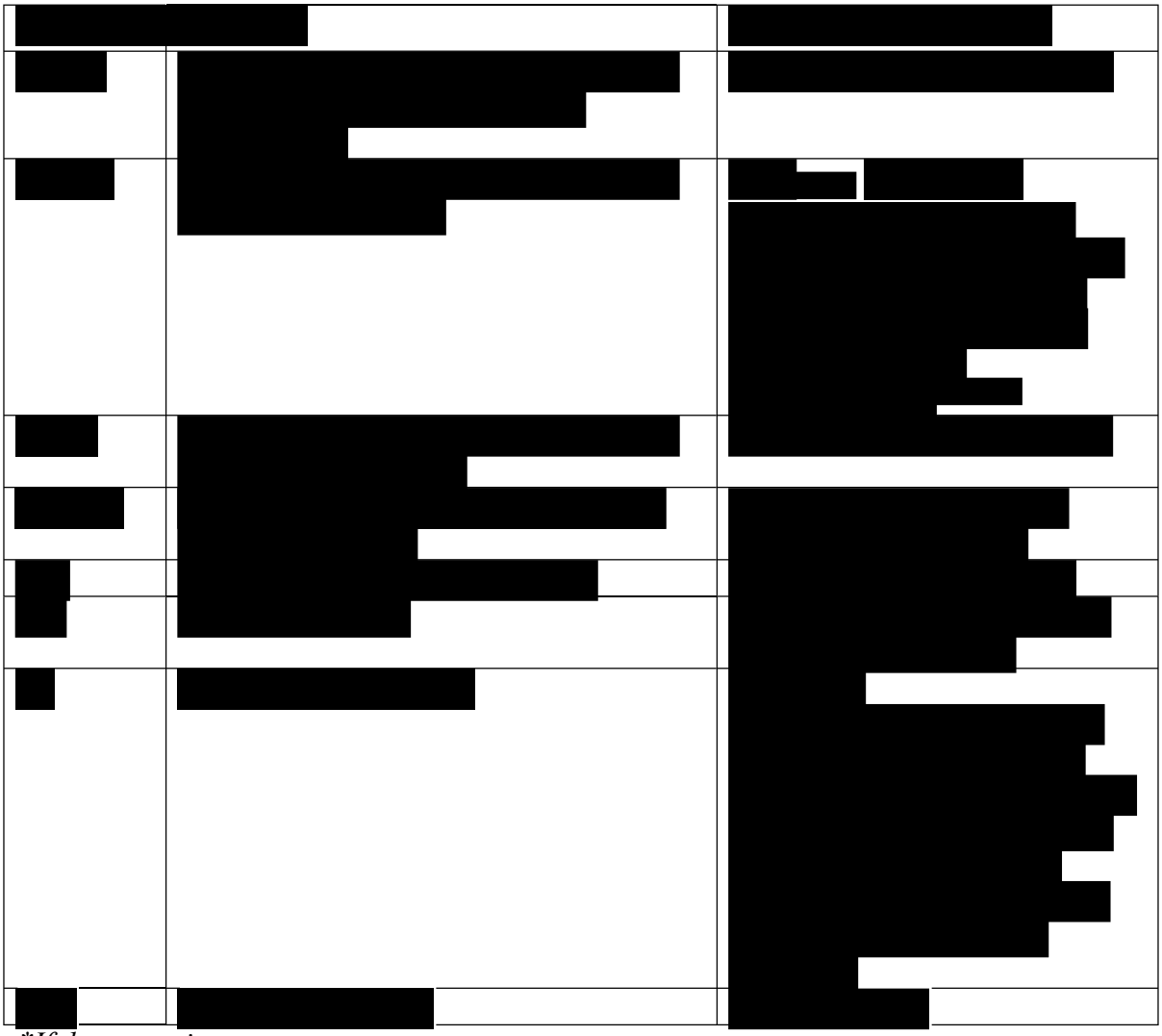

**If data permit.*

Safety and tolerability data will also be evaluated and are discussed in Section 3.5.

3.4. Baseline Variables

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

3.5. Safety Endpoints

The following data are considered in standard safety summaries (see protocol for collection days, baseline assessment, and list of parameters):

- adverse events (AE)

- laboratory data
- vital signs data
- ECG results

3.5.1. Adverse Events

Any adverse events occurring following start of treatment will be considered as treatment emergent adverse event (TEAE). Events that occur during follow-up within the lag time of up to 28 days after the last tafamidis dose will be counted as treatment emergent and attributed to the last treatment taken. Events that occur during the washout period (up to 28 days from the last treatment) between study periods will be counted as treatment emergent and attributed to the previous treatment taken. The time period for collecting AEs ("active collection period") for each participant begins from the time the participant provides informed consent.

3.5.2. Laboratory Data

Safety laboratory tests will be performed as described in the protocol. To determine if there are any clinically significant laboratory abnormalities, the haematological, clinical chemistry (serum) and urinalysis safety tests will be assessed against the criteria specified in the sponsor reporting standards. The assessment will not take into account whether each participants's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

For each period, the baseline measurement is the predose measurement on Day -1.

3.5.3. Vital Signs

Seated blood pressure (BP), pulse rate (PR), and temperature will be measured at times specified in the SoA given in the protocol.

The baseline measurement is the predose measurement on Day 1 Period 1.

3.5.4. Electrocardiograms

QT interval, QTcF, PR, QRS and heart rate (HR) will be recorded at each assessment time indicated in the SoA given in the protocol. QTcF will be derived using Fridericia's heart rate correction formula:

$$QTcF = QT / (RR)^{(1/3)} \text{ where } RR = 60/HR \text{ (if not provided)}$$

The baseline measurement is the predose measurement on Day 1 Period 1.

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.*
Safety analysis set	*All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.*
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.*
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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

The alternative hypothesis of bioequivalence (H1: $q_L \leqslant m_T - m_R \leqslant q_U$), and the null hypothesis of inequivalence (Ho: $m_T - m_R < q_L$ or $m_T - m_R > q_U$) can be expressed as the following 2 separate one-sided hypotheses:

HoA: $m_T - m_R < q_L$

H1A: $q_L \leqslant m_T - m_R$

HoB: $m_T - m_R > q_U$

H1B: $m_T - m_R \leqslant q_U$

[redacted]

where m_T and m_R represent the average bioavailability on a log scale for the Test and Reference products respectively and $[q_L, q_U]$ defines the bioequivalence range.

Bioequivalence of the Test treatment to Reference treatment will be concluded if the 90% confidence intervals for the ratios of adjusted geometric means for tafamidis AUC_{inf} (if data permit, otherwise AUC_{last}) and C_{max} fall entirely within the acceptance region of (80%, 125%).

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.

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5.3.2. Safety Data

Missing values in standard summaries of AEs, laboratory data, vital signs, and ECGs will be imputed according to CaPS.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

For assessment of the bioequivalence objective of the study (Periods 1 and 2), 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 (12.2 mg tafamidis free acid tablet) will be the Test treatment, while Treatment B (commercial 20 mg tafamidis meglumine softgel capsule) will be the Reference treatment.

Bioequivalence of the 2 formulations will be concluded if the 90% confidence intervals for the ratio of adjusted geometric means for both AUC_{inf} (if data permit, otherwise AUC_{last}) and C_{max} fall wholly within (80%, 125%).

For assessment of the food effect objective of the study (where treatment comparison occurs via fixed-sequence), natural log transformed AUC_{inf}, AUC_{last}, AUC_{72} and C_{max} will be analyzed separately using a mixed effect model with treatment as fixed effects and participant 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 C (12.2 mg tafamidis free acid tablet, fed) will be the Test treatment, while Treatment A (12.2 mg tafamidis free acid tablet, fasted) 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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	[redacted]
	[redacted]

[redacted]

6.3. Subset Analyses

There are no planned subset analyses.

6.4. Baseline and Other Summaries and Analyses

6.4.1. Demographic Summaries

Demographic 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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6.5.1. Adverse Events

Adverse events will be reported in accordance with the CaPS.

Participant discontinuations due to adverse events will be detailed by treatment. Data will be reported in accordance with the CaPS.

6.5.2. Laboratory Data

Laboratory data will be listed and summarized by treatment in accordance with the CaPS.

6.5.3. Vital Signs

Vital sign data will be databased and available upon request.

6.5.4. Electrocardiograms

ECG data will be databased and available upon request.

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 Analyses

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;
where trt in ("A", "B");
        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: 12.2 mg tafamidis free acid tablet, fasted (Test)
B: Commercial 20 mg tafamidis meglumine soft gelatin capsule, fasted (Reference)          */
```

For secondary objective: Treatment C (Test) vs Treatment A (Reference)

```
proc mixed data=tab.pk;
where trt in ("A", "C");
        class trt participant;
        model l&var=trt / ddfm=KR;
        random participant / subject=participant;
        lsmeans trt;
        estimate 'C vs A' 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: 12.2 mg tafamidis free acid tablet, fasted (Reference)
C: 12.2 mg tafamidis free acid tablet, fed (Test)        */
```

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
$AUMC_{inf}$	area under the first moment curve from zero time to infinity
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
m_R	the average bioavailability on a log scale for the Reference product
CCI	[redacted]
m_T	the average bioavailability on a log scale for the Test product
N/A	not applicable
NC	not calculated
ND	not done
NS	no sample
PK	pharmacokinetic(s)
PR	pulse rate
q_L	lower limit of bioequivalence
QRS	Combination of Q-, R- and S- wave on an electrocardiogram representing ventricular depolarization
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
q_U	upper limit of bioequivalence
RR	respiratory rate
SAP	statistical analysis plan
SD	standard deviation
SoA	schedule of activities

Abbreviation	Term
CCI [redacted]	[redacted]
TEAE	treatment emergent adverse event
t_{last}	time of last measurable concentration
CCI [redacted]	[redacted]