CLINICAL STUDY REPORT SYNOPSIS

Study Title:	A Phase 1, Open-Label, Randomized, Three-Treatment, Three-Period, Crossover, Single Dose Study to Estimate the Relative Bioavailability of 61 mg and 70 mg Tafamidis Free Acid Tablets to Commercial 61 mg Tafamidis Free Acid Capsule Administered Under Fasted Conditions in Healthy Adult Participants
Study Number:	B3461114
Study Phase:	1
Regulatory Agency or Public Disclosure Identifier Number:	NCT #: NCT06273839 EU CT #: 2023-509241-12-00
Pediatric Investigational Plan Number:	Not Applicable
Study Intervention:	Tafamidis (PF-06291826)
Trade Name	Vyndamax® / Vyndaqel®
Indication:	Transthyretin Amyloidosis (ATTR)
Study Sponsor:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001
Study Initiation Date (FPFV):	27 February 2024
Primary Completion Date (PCD):	27 May 2024
Presentation of data in this CSR synopsis based on: **Study Completion (LPLV) Date:**	27 May 2024
Early Termination Status	This study was not terminated early and was completed as per protocol.
CSR Version and Report Date:	**Document Version** / **Report Date** Final LPLV CSR Version 1.0 / 20 September 2024

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GOOD CLINICAL PRACTICE STATEMENT

This study was conducted in compliance with GCP guidelines and, where applicable, local country regulations relevant to the use of new therapeutic agents in the country of conduct, including the archiving of essential documents.

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Number of Study Center(s) and Investigator(s):

This study was conducted at 1 site in Belgium.

A list of study center and investigators involved in this study is provided in Appendix 16.1.4.1.

Publications: None

Brief Description of The Trial Design and Methodology:

This study was a Phase 1, open-label, randomized, 3-treatment, 3-period, crossover, single dose study to estimate the relative bioavailability of tafamidis 61 mg free acid tablet (Test 1) and tafamidis 70 mg free acid tablet (Test 2) to tafamidis 61 mg free acid capsule (Reference) administered under fasted conditions in healthy adult participants.

There were 3 treatment periods (Periods 1, 2 and 3). A total of approximately 12 participants were to be enrolled. Approximately 2 participants were to be randomized into 1 of 6 treatment sequences. On Day 1 of each period, participants received a single dose of one of the 3 tafamidis formulations according to the treatment sequence schema provided in Table S1. Participants were to be fasted 10 hours prior to dosing and 4 hours post-dosing. Participants were admitted to the Pfizer Clinical Research Unit (PCRU) at least 12 hours prior to dosing on Day 1 (ie, on Day -1) and were required to stay in the PCRU for 4 or 8 days, at discretion of the investigator, in each period.

Table S1. Treatment Sequence Schema

Sequence	Period 1	Period 2	Period 3
1 (n=2)	A	B	C
2 (n=2)	B	C	A
3 (n=2)	C	A	B
4 (n=2)	A	C	B
5 (n=2)	B	A	C
6 (n=2)	C	B	A

Treatment A = 1 × tafamidis 61 mg free acid tablet (Test 1).
Treatment B = 1 × tafamidis 61 mg free acid capsule (Reference).
Treatment C = 1 × tafamidis 70 mg free acid tablet (Test 2).

Number of Participants (Planned and Analyzed):

Table S2. Number of Participants (Planned and Analyzed)

Population	N	Definition
Planned	12	Healthy participants aged ≥18 years.
Enrolled	12	"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 was considered enrolled if the informed consent was not withdrawn prior to participating in any study activity after screening.

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Table S2. Number of Participants (Planned and Analyzed)

Safety Analysis Set	12	All participants randomly assigned to study intervention and who took at least 1 dose of study intervention.
Pharmacokinetic(s) (PK) Concentration Set	12	All participants who received at least 1 dose of tafamidis and who had at least 1 measurable concentration of tafamidis.
PK Parameter Set	12	All participants who received at least 1 dose of tafamidis and who had at least 1 of the PK parameters of interest calculated.

Diagnosis and Main Criteria for Inclusion and Exclusion:

This study enrolled healthy participants aged ≥18 years with body mass index (BMI) of 16 – 32 kg/m^2. Participants with evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease were excluded from the study.

Study Intervention:

On Day 1 of each period, each participant received either 1 tafamidis 61 mg free acid tablet (Treatment A, Test 1) or 1 tafamidis 70 mg free acid tablet (Treatment C, Test 2) or 1 tafamidis 61 mg free acid capsule (Treatment B, Reference) under fasted conditions (following an overnight fast of at least 10 hours).

The manufacturing lot numbers for the study intervention(s) administered in this study are provided in Table S3.

Table S3. Study Intervention(s) Lot Number(s)

Investigational Product Description	Vendor Lot Number	Pfizer Lot Number	Strength / Potency	Dosage Form
Tafamidis 61.0 mg Size 9.5 Oblong Opaque Reddish Brown Unprinted Soft Gelatin Capsule	5366799	23-DP-01479	61 mg	Capsule
Tafamidis 61 mg Round Debossed White Film Coated Tablet (Titanium Free)	HK7731	23-DP-01775	61 mg	Tablet
Tafamidis 70 mg Round Plain Faced White Film Coated Tablet (Titanium Free)	HK7728	23-DP-01777	70 mg	Tablet

Global Substantial Modifications:

Not applicable.

Global Interruptions and Re-starts:

Not applicable.

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Endpoints and Statistical Methods:

Table S4. Objectives, Endpoints, and Statistical Methods

Objectives	Endpoints	Analysis Type	Analysis Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Primary:					
To estimate the relative bioavailability of 61 mg tafamidis free acid tablet (Test 1) and 70 mg tafamidis free acid tablet (Test 2) to 61 mg tafamidis free acid capsule (Reference) in fasted healthy participants.	AUC_{inf} (if data permitted, otherwise AUC_{last}) and C_{max} of tafamidis.	Primary PK Analysis	PK Parameter Set and PK Concentration Set	In all data presentations (except listings), concentrations BLQ were set to 0. In listings, BLQ values were reported as "<LLOQ". In summary tables and plots of median profiles, statistics were to be calculated having set concentrations to missing if 1 of the following cases was true: 1. A concentration had been collected as ND or NS. 2. A deviation in sampling time was of sufficient concern or a concentration had been flagged as anomalous by the pharmacokineticist. Summary statistics were not to be presented at a particular time point if more than 50% of the data were missing. Actual PK sampling times were used in the derivation of PK parameters. If a PK parameter could not be derived from a participant's concentration data, the parameter was coded as NC. In summary tables, statistics were calculated by setting NC values to missing; and statistics were presented for a particular treatment with ≥3 evaluable measurements. PK parameter analyses were not to be performed for a particular parameter if more than 50% of the data were NC.	Mixed effect model with sequence, period and treatment as fixed effects and participant within sequence as a random effect
Abbreviations: AUC_{inf} = area under the plasma concentration-time curve from time 0 extrapolated to infinite time; AUC_{last} = area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration; BLQ = below the limit of quantification; C_{max} = maximum plasma concentration; LLOQ = lower limit of quantification; NC = not calculated; ND = not done; NS = no sample.					

SUMMARY OF RESULTS:

Participant Disposition:

A total of 12 participants were randomized and treated with 3 treatments of tafamidis 61 mg free acid tablet (Test 1), tafamidis 70 mg free acid tablet (Test 2) and tafamidis 61 mg free acid capsule (Reference), with 2 participants each randomized to receive 1 of the 6 treatment sequences shown in Table S1. All 12 participants completed the follow-up.

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Demographic and Other Baseline Characteristics:

A total of 12 male participants were enrolled and randomized at PCRU in Brussels, Belgium.

- 11 (91.7%) participants were White and 1 (8.3%) participant was Black or African American.
- The mean (standard deviation [SD]) age was 46.0 (13.99) years: 5 (41.7%) participants were 18 – 44 years of age, 6 (50.0%) participants were 45 – 64 years of age and 1 (8.3%) participant was 65 – 84 years of age.
- The mean (SD) BMI was 25.35 (2.36) kg/m^2.

Exposure:

All 12 randomized participants received a single dose of tafamidis on Day 1 of Periods 1, 2 and 3 according to the treatment sequence schema in Table S1.

Summary of PK and Adverse Event (AE) Results:

Table S5. Study B3461114 PK and AE Results

Endpoints	Results
Primary:	
AUC_{inf} (if data permitted, otherwise AUC_{last}) and C_{max} of tafamidis.	The ratio of adjusted geometric means (90% confidence interval [CI]) of tafamidis AUC_{inf} and C_{max} were 96.94% (88.79%, 105.84%) and 97.64% (86.57%, 110.13%), respectively, following a single oral administration of tafamidis 61 mg free acid tablet (Test 1) relative to the 61 mg free acid capsule (Reference). The ratio of adjusted geometric means (90% CI) of tafamidis AUC_{inf} and C_{max} were 119.02% (109.01%, 129.94%) and 104.63% (92.77%, 118.01%), respectively, following a single oral administration of tafamidis 70 mg free acid tablet (Test 2) relative to the 61 mg free acid capsule (Reference).
Summary of AEs:	
The incidences of TEAEs were comparable across the 3 treatment groups, and all TEAEs were non-serious. • In the tafamidis 61 mg free acid tablet group (Test 1), 2 TEAEs were reported in 2 (16.7%) participants, of which 1 was a treatment-related TEAE. • In the tafamidis 70 mg free acid tablet group (Test 2), 3 TEAEs were reported in 3 (25.0%) participants, and none of these TEAEs was related to study intervention as assessed by the investigator. • In the tafamidis 61 mg free acid capsule group (Reference), 3 TEAEs were reported in 2 (16.7%) participants, of which 1 was a treatment-related TEAE.	

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CONCLUSIONS:

PK:

- The 90% CIs for the ratios (61 mg tablet [Test 1]/61 mg capsule [Reference]) of the adjusted geometric means of tafamidis were contained within the acceptance criteria for bioequivalence (80% – 125%) for AUC_{inf} and C_{max}.

- The 90% CIs for the ratios (70 mg tablet [Test 2]/ 61 mg capsule [Reference]) of the adjusted geometric means of tafamidis were contained within the acceptance criteria for bioequivalence (80% – 125%) for C_{max}; however, the AUC_{inf} of tafamidis fell outside the upper boundary of the 90% CI.

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