Title Page

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

Study Intervention Number:	PF-06291826
Study Intervention Name:	Tafamidis
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Pediatric Investigational Plan Number:	Not Applicable
Protocol Number:	B3461103
Phase:	1

Brief Title: Phase 1 Study to Determine 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

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: 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

Brief Title: Phase 1 Study to Determine 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 Bioavailabilty in Healthy Adult Participants

Regulatory Agency Identification Number(s):

US IND Number:	CCI
EudraCT Number:	Not Applicable
ClinicalTrials.gov ID:	Not Available
Pediatric Investigational Plan Number:	Not Applicable
Protocol Number:	B3461103
Phase:	1

Rationale:

This study will be conducted to determine if a 12.2 mg tafamidis free acid tablet (Test) 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.

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]

Overall Design:

This is 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.

Number of Participants:

The sample size of 22 participants (11 participants per sequence in the fasted arms) to ensure a minimum of 18 PK evaluable participants for this 3-way crossover will provide 95% power that the 90% confidence interval for the ratio of Test to Reference for AUC_{inf} will lie within the acceptance region of (80%, 125%) and 89% power that 90% confidence interval for the ratio of Test to Reference treatment for C_{max} will lie within the acceptance region of (80%, 125%). Consequently, this study has approximately 85% power overall to demonstrate bioequivalence of the Test treatment to the Reference treatment [ie, equivalence in both AUC_{inf} and C_{max}]. This estimate is based on the assumption that the true ratio between Test and Reference treatments for both AUC_{inf} and C_{max} is 0.9.

The power calculations assumed the estimates of within participant standard deviations of 0.098 and 0.119 for $\log_e AUC_{inf}$ and $\log_e C_{max}$, respectively, obtained as an average from studies B3461030, B3461044 and B3461095.

Study Population:

Inclusion and exclusion criteria are listed below:

Inclusion Criteria

Participants must meet the following inclusion criteria to be eligible for enrollment into the study:

1. Participants aged 18 years or older (or the minimum age of consent in accordance with local regulations) at screening.

2. Healthy female participants of nonchildbearing potential and/or male participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, and laboratory tests.

3. BMI of 17.5 to 30.5 kg/m^2; and a total body weight >50 kg (110 lb).

Exclusion Criteria

Participants with any of the following characteristics/conditions will be excluded:

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

    - Any condition possibly affecting drug absorption (eg, gastrectomy, cholecystectomy).

    - History of HIV infection, hepatitis B, or hepatitis C; positive testing for HIV, HBsAg, HBcAb, or HCVAb. Hepatitis B vaccination is allowed.

    - Hypersensitivity to any component of the formulations

2. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality or other conditions or situations related to COVID-19 pandemic (eg, Contact with positive case, residence, or travel to an area with high incidence) that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

3. Use of prescription or nonprescription drugs, dietary and herbal supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. (Refer to Section 6.9 Prior and Concomitant Therapy for additional details).

4. Current use of any prohibited concomitant medication(s) or participant unwilling/unable to use a permitted concomitant medication(s). Refer to Section 6.9 Prior and Concomitant Therapy.

5. Previous administration with an investigational product (drug or vaccine) within 6 months (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

6. A positive urine drug test.

7. Screening seated BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of seated rest. If BP is ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participant's eligibility.

8. Standard 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, QTcF >450 ms, complete LBBB, signs of an acute or indeterminate- age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third- degree AV block, or serious bradyarrhythmias or tachyarrhythmias). If the uncorrected QT interval is >450 ms, this interval should be rate-corrected using the Fridericia method only and the resulting QTcF should be used for decision making and reporting. If QTcF exceeds 450 ms, or QRS exceeds 120 ms, the ECG should be repeated twice and the average of the 3 QTcF or QRS values used to determine the participant's eligibility. Computer-interpreted- ECGs should be overread by a physician experienced in reading ECGs before excluding a participant.

9. Participants with **ANY** of the following abnormalities in clinical laboratory tests at screening, as assessed by the study-specific laboratory and confirmed by a single repeat test, if deemed necessary:

   - AST **or** ALT level ≥ 1.5 × ULN;

   - Total bilirubin level ≥1.5 × ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN.

10. History of alcohol abuse or binge drinking and/or any other illicit drug use or dependence within 6 months of Screening. Binge drinking is defined as a pattern of 5 (male) and 4 (female) or more alcoholic drinks in about 2 hours. As a general rule, alcohol intake should not exceed 14 units per week (1 unit = 8 ounces (240 mL) beer, 1 ounce (30 mL) of 40% spirit, or 3 ounces (90 mL) of wine).

11. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing.

12. History of sensitivity to heparin or heparin-induced thrombocytopenia.

13. Unwilling or unable to comply with the criteria in the Lifestyle Considerations section of this protocol.

14. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

Study Arms and Duration:

Eligible participants who continue to meet entry criteria will be admitted to the CRU on Day -1 and will be required to stay in the CRU for 8 overnight stays in each period. All participants will be discharged from the CRU following completion of the discharge evaluation, which includes adverse event monitoring, physical examination (at investigator discretion), vital signs, ECG measurements, and safety laboratory tests.

Study Intervention(s)			
Intervention Name	Tafamidis free acid tablet (fasted)	Tafamidis meglumine soft gelatin capsule (fasted)	Tafamidis free acid tablet (fed)
Arm Name (group of participants receiving a specific treatment or no treatment)	Treatment A	Treatment B	Treatment C
Unit Dose Strength(s)	12.2 mg	20 mg	12.2. mg
Route of Administration	Oral	Oral	Oral
Use	Experimental	Experimental	Experimental
IMP or NIMP/AxMP	IMP	IMP	IMP

Study Arm(s)			
Arm Title	Treatment A	Treatment B	Treatment C
Arm Type	Test - fasted	Reference – fasted	Test - fed
Arm Description	Participants will receive a single 12.2 mg tafamidis free acid tablet, fasted	Participants will receive a single commercial 20 mg tafamidis meglumine capsule	Participants will receive a single 12.2 mg tafamidis free acid tablet, fed

Statistical Methods:

Natural log-transformed AUC_{inf}, AUC_{last}, CCI, 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 fasted) will be the Test treatment, while Treatment B (commercial 20 mg tafamidis meglumine softgel capsule fasted) will be the Reference treatment.

Bioequivalence of between 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 AUClast) and C_{max} fall wholly within the pre-specified criteria (80%, 125%).

For the food effect comparison, 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.

The PK parameters AUC_{inf}, C_{max}, AUC_{last}, CCI of tafamidis will be summarized descriptively by treatment. For AUC_{inf}, AUC_{last}, and C_{max}, individual participant parameters will be plotted against treatment. Concentrations will be listed and summarized descriptively by treatment and PK sampling time. Individual participant, mean and median profiles of the concentration-time data will be plotted by treatment. For summary statistics and median plots by sampling time, the nominal PK sampling time will be used. For individual participant plots by time, the actual PK sampling time will be used.

Ethical Considerations:

Participants will be expected to commit time and may experience some discomfort while undergoing study assessments. In addition, participants must avoid vaccination with live attenuated vaccines throughout the study. When relevant, it is recommended that participants keep their diet habits constant throughout the study.

1.2. Schema

Not applicable.

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Section 10.10	Screen	Periods 1, 2 and 3									F/U	Early Term Discont	Notes
		Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	28-35 days		• All screening should be done ≤ 28 days before the first dose. • Day relative to start of study intervention (Day 1). • At least a 16 day washout interval between Day 1 in each subsequent period. • Follow-up may occur via telephone contact and must occur 28 to 35 days after administration of the final dose of study intervention.
Informed consent	X												• Informed consent should be obtained prior to undergoing any study-specific procedures. • See Schedule of Activities
CRU confinement		X	→	→	→	→	→	→	→				
Inclusion/exclusion criteria	X	X											• Period 1 only.
Demography	X												
Medical/medication history	X	X											• Review medical, drug, alcohol, and tobacco history predose to determine any change from Screening evaluation (Period 1 only).

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Section 10.10	Screen	Periods 1, 2 and 3									F/U	Early Term/ Discont	Notes
		Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	28-35 days		• All screening should be done ≤ 28 days before the first dose. • Day relative to start of study intervention (Day 1). • At least a 16 day washout interval between Day 1 in each subsequent period. • Follow-up may occur via telephone contact and must occur 28 to 35 days after administration of the final dose of study intervention.
CCI													
FSH (postmenopausal females only)	X												• Serum FSH concentrations for any female who has been amenorrheic for at least 12 consecutive months.
Urine drug testing	X	X											

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Section 10.10	Screen	Periods 1, 2 and 3									F/U	Early Term Discont	Notes
		Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	28-35 days		• All screening should be done ≤ 28 days before the first dose. • Day relative to start of study intervention (Day 1). • At least a 16 day washout interval between Day 1 in each subsequent period. • Follow-up may occur via telephone contact and must occur 28 to 35 days after administration of the final dose of study intervention.
CCI [redacted]	[redacted]		[redacted]							[redacted]		[redacted]	[redacted]
[redacted]	[redacted]		[redacted]							[redacted]		[redacted]	[redacted]
HIV, HBsAg, HBcAb, HCVAb	X												
COVID-19 questionnaire	X	X											• Check exposure to positive subject, residence or travel in area of high incidence, and COVID-19 related signs and symptoms. To be done at check in of each visit.

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Section 10.10	Screen	Periods 1, 2 and 3									F/U	Early Term Discont	Notes
		Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	28-35 days		• All screening should be done ≤ 28 days before the first dose. • Day relative to start of study intervention (Day 1). • At least a 16 day washout interval between Day 1 in each subsequent period. • Follow-up may occur via telephone contact and must occur 28 to 35 days after administration of the final dose of study intervention.
COVID-19 testing	X	X				X							• The testing for COVID-19 pathogen will be performed at each visit per local site procedures. For participants admitted for residence, a subsequent COVID-19 test will be performed after 4 days (ie, upon completion of 4 x 24 hours in house), or if they develop COVID-19 like symptoms.
COVID-19 check temperature	X	X	X	X	X	X	X	X	X	X			• To be done at least daily during residence.
Study intervention administration			X										• Participants fasted overnight (minimum of 10 hours) prior to dosing and for 4 hours postdose on Day 1 (Periods 1 and 2 only).
Pharmacokinetic blood sampling			X	X	X	X	X	X	X	X		X	• Final visit procedures will be performed on the last day of the last period (Day 8 Period 3), or upon study discontinuation.

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Section 10.10	Screen	Periods 1, 2 and 3									F/U	Early Term Discont	Notes
		Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	28-35 days		• All screening should be done ≤ 28 days before the first dose. • Day relative to start of study intervention (Day 1). • At least a 16 day washout interval between Day 1 in each subsequent period. • Follow-up may occur via telephone contact and must occur 28 to 35 days after administration of the final dose of study intervention.
CCI [redacted]		[redacted]											[redacted]
Serious and non-serious AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	• See Section 8.4.3 for follow-up AE and SAE assessments.
Prior/concomitant medication and treatments	X	X	X	X	X	X	X	X	X	X	X	X	
CRU discharge										X			

Pharmacokinetic Sampling Schema

Visit Identifier	**Periods 1-3**																	**Notes**
Study Day	**1**									**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Early Term/ Discont**	
Hours Before/After Dose	**0**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**12**	**24**	**48**	**72**	**96**	**120**	**144**	**168**		Hour 0 = predose sample collection
Study intervention administration	X																	
PK blood sampling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

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.

2.1. Study Rationale

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.

2.2. Background

Amyloidosis is a severely debilitating, and ultimately fatal, systemic condition induced by the accumulation of an insoluble fibrillar protein (amyloid) within tissues in amounts sufficient to impair normal function.

The tafamidis salt (tafamidis meglumine, Vyndaqel®) 20 mg QD is approved in more than 40 countries worldwide for the treatment of patients with ATTR-PN to delay neurologic impairment.

In addition, the tafamidis salt (tafamidis meglumine, Vyndaqel) 80 mg QD is approved in the US and Japan, among other countries, for the treatment of patients with ATTRCM. The 80 mg dose is administered as 4 × 20 mg tafamidis meglumine soft gelatin capsules. A tafamidis free acid 61 mg single oral dosage form is also approved in the US (tafamidis, Vyndamax®) and EU (tafamidis, Vyndaqel), among other countries, to facilitate patient convenience.

CCI [redacted]

CCI

[redacted]

2.3. Benefit/Risk Assessment

Tafamidis is not expected to provide any clinical benefit to healthy participants. This study is designed primarily to generate BE data to support a formulation change.

In completed clinical studies, tafamidis was determined to be well-tolerated and to have an acceptable safety profile. More detailed information about the known and expected benefits and risks and reasonably expected AEs of tafamidis may be found in the IB[i], which is the SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s)		
Sorbitol is an inactive ingredient present in tafamidis meglumine 20 mg capsules.	Each capsule contains no more than 44 mg of sorbitol, which, based on a 70 kg body weight, is equivalent to 0.63 mg/kg/day for tafamidis meglumine 20 mg dose (1 capsule).	Sorbitol (E 420) is a source of fructose and should be taken into account when monitoring dietary intake of sorbitol or fructose.
Potential risks of liver abnormalities	Risk is based on observations in animal studies (IB[i] Section 7.11.1.2 - Hepatotoxicity).	Study will monitor liver enzymes at screening and during the study: AST, ALT, total bilirubin, alkaline phosphatase (Section 10.3 - Table 5).
Potential risks of reproductive toxicity (abnormalities in babies exposed to tafamidis during pregnancy)	Risk is based on observations in animal studies (IB[i] Section 7.11.2.2. Reproductive Toxicity).	Study will only enroll females who are not of child bearing potential (Section 5.1 _Item 2).
Other *potential risk:*		
The COVID-19 pandemic may pose risks to study participation.	Participants may have increased risk of SARS-CoV-2 infection by undergoing a study procedure at a study facility.	Inclusion of COVID-19 specific assessments according to the SoA.

2.3.2. Overall Benefit/Risk Conclusion

Taking into account the measures to minimize risk to study participants, the potential risks identified in association with tafamidis or study procedures are justified by the anticipated benefits that may be afforded to patients with ATTR-CM and/or ATTR-PN.

3. 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]

4. STUDY DESIGN

4.1. Overall 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.

Screening evaluation will occur within 28 days prior to the first dose in Period 1. Participants will be admitted to the CRU at least 12 hours prior to dosing on Day 1 and will be required to stay in the CRU for 8 days in each period. 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. 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. Participants are to be fasted 10 hours prior to dosing (excluding fed arm) and 4 hours post-dosing. For the administration, the drug products will be administrated with 240 mL of

water. Medication will be administered at approximately 8:00 AM ±2 hours on Day 1 of each period according to a computer-generated randomization schedule.

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 (Fed)
1 (n = 11)	A	B	C
2 (n = 11)	B	A	C

The study medications are listed in Table 3.

Table 3. Description of Tafamidis Treatment

Treatment	Study Medication
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

The 12.2 mg tafamidis free acid tablet and commercial 20 mg tafamidis meglumine capsules will be supplied by Pfizer Worldwide Research and Development.

4.2. Scientific Rationale for Study Design

This study was designed to characterize the BE of a 12.2 mg tafamidis free acid tablet compared to the commercial 20 mg tafamidis meglumine soft gelatin capsule in healthy participants under fasted conditions and to estimate the effect of food on the 12.2 mg tafamidis free acid tablet.

4.2.1. Choice of Contraception/Barrier Requirements

Tafamidis is approved for use in ATTR-PN and ATTR-CM without any contraceptive precautions. There is no suspicion of human teratogenicity based on the intended pharmacology.

4.2.2. Collection of Retained Research Samples

Retained Research Samples will be collected and stored for further analyses which may, for example, provide greater understanding of the study intervention.

4.3. Justification for Dose

The 12.2 mg free acid tablet contains the same API as the tafamidis meglumine 20 mg formulation. One tafamidis meglumine 20 mg capsule contains 12.2 mg of tafamidis free acid.

Tafamidis meglumine 20 mg is currently available as a soft gelatin capsule approved for the treatment of ATTR-PN (20 mg) and ATTR-CM (4 x 20 mg).

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the trial.

A participant is considered to have completed the study if they have completed all periods of the study, including the last visit or the last scheduled procedure shown in the SoA.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. Use of a prescreening tool is utilized for study recruitment purposes, it will include collection of information that reflects the enrollment of a diverse participant population including, where permitted under local regulations, age, sex, and race, and ethnicity. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Participants aged 18 years or older (or the minimum age of consent in accordance with local regulations) at screening.

2. Healthy female participants of nonchildbearing potential and/or male participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, and laboratory tests.

Other Inclusion Criteria:

3. BMI of 17.5 to 30.5 kg/m^2; and a total body weight >50 kg (110 lb).

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

- Any condition possibly affecting drug absorption (eg, gastrectomy, cholecystectomy).

- History of HIV infection, hepatitis B, or hepatitis C; positive testing for HIV, HBsAg, HBcAb, or HCVAb. Hepatitis B vaccination is allowed.

- Hypersensitivity to any component of the formulations

2. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality or other conditions or situations related to COVID-19 pandemic (eg, Contact with positive case, residence, or travel to an area with high incidence) that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

3. Use of prescription or nonprescription drugs, dietary and herbal supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. (Refer to Section 6.9 Prior and Concomitant Therapy for additional details).

4. Current use of any prohibited concomitant medication(s) or participant unwilling/unable to use a permitted concomitant medication(s). Refer to Section 6.9 Prior and Concomitant Therapy.

Prior/Concurrent Clinical Study Experience:

5. Previous administration with an investigational product (drug or vaccine) within 6 months (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

Diagnostic Assessments:

6. A positive urine drug test.

7. Screening seated BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of seated rest. If BP is ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participant's eligibility.

8. Standard 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, QTcF >450 ms, complete LBBB, signs of an acute or indeterminate- age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third- degree AV block, or serious bradyarrhythmias or tachyarrhythmias). If the uncorrected QT interval is >450 ms, this interval should be rate-corrected using the Fridericia method

only and the resulting QTcF should be used for decision making and reporting. If QTcF exceeds 450 ms, or QRS exceeds 120 ms, the ECG should be repeated twice and the average of the 3 QTcF or QRS values used to determine the participant's eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding a participant.

9. Participants with **ANY** of the following abnormalities in clinical laboratory tests at screening, as assessed by the study-specific laboratory and confirmed by a single repeat test, if deemed necessary:

   - AST **or** ALT level ≥ 1.5 × ULN;
   - Total bilirubin level ≥1.5 × ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN.

Other Exclusion Criteria:

10. History of alcohol abuse or binge drinking and/or any other illicit drug use or dependence within 6 months of Screening. Binge drinking is defined as a pattern of 5 (male) and 4 (female) or more alcoholic drinks in about 2 hours. As a general rule, alcohol intake should not exceed 14 units per week (1 unit = 8 ounces (240 mL) beer, 1 ounce (30 mL) of 40% spirit, or 3 ounces (90 mL) of wine).
11. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing.
12. History of sensitivity to heparin or heparin-induced thrombocytopenia.
13. Unwilling or unable to comply with the criteria in the Lifestyle Considerations section of this protocol.
14. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.
15. Use of tobacco or nicotine-containing products in excess of the equivalent of 5 cigarettes per day.

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations and 10 hours prior to the collection of the predose PK sample (Treatments A and B).

- Water is permitted until 1 hour prior to study intervention administration. For investigational product administered in the fed state (Treatment C), water may be allowed with breakfast prior to the dose.

- Water may be consumed without restriction beginning 1 hour after dosing. Noncaffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices—see below) may be consumed with meals and the evening snack.

- If participants are assigned to a fed condition study period, they will be given a high-fat, high-calorie breakfast on Day 1 of that period, and a standardized breakfast on all other days of that period. A Food and Drug Administration (FDA) recommended breakfast of a high-fat (approximately 50% of total caloric content of the meal), high calorie (approximately 800-1000 calories) meal will be given on Day 1. A representative example of a high-fat, high-calorie meal would be: 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 100 g of hash brown potatoes, 8 fluid ounce (240 mL) of whole milk (ie, approximately 150 protein calories, 250 carbohydrate calories, 500-600 fat calories).

- Lunch will be provided approximately 4 hours after dosing.

- Dinner will be provided approximately 9 to 10 hours after dosing.

- An evening snack may be permitted.

- Participants will refrain from consuming red wine, grapefruit, or grapefruit-related citrus fruits (eg, Seville oranges, pomelos, fruit juices) from 7 days prior to the first dose of study intervention until collection of the final PK blood sample.

- Except during the fed condition, while participants are confined, their total daily nutritional composition should be approximately 55% carbohydrate, 30% fat, and 15% protein. The daily caloric intake per participant should not exceed approximately 3200 kcal.

5.3.2. Caffeine, Alcohol, and Tobacco

- Participants will abstain from caffeine-containing products for 24 hours prior to the start of dosing until collection of the final PK sample of each study period.

- Participants will abstain from alcohol for 24 hours prior (or as specified above for red wine) to admission to the CRU and continue abstaining from alcohol until collection of the final PK sample of each study period. Participants may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.

- Participants will abstain from the use of tobacco- or nicotine-containing products for 24 hours prior to dosing and during confinement in the CRU.

5.3.3. Activity

- Participants will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted;

- In order to standardize the conditions on PK sampling days, participants will be required to refrain from lying down (except when required for BP, pulse rate, and ECG measurements), eating, and drinking beverages other than water during the first 4 hours after dosing;

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. Screen failure data are collected and remain as source and are not reported on the CRF.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational and medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

For the purposes of this protocol, study intervention refers to 12.2 mg tafamidis free acid tablets and commercial 20 mg tafamidis meglumine capsules.

6.1. Study Intervention(s) Administered

Eligible participants who continue to meet entry criteria will be admitted to the CRU on Day -1 and will be required to stay in the CRU for 8 overnight stays in each period. All participants will be discharged from the CRU following completion of the discharge evaluation, which includes adverse event monitoring, physical examination (at investigator discretion), vital signs, ECG measurements, and safety laboratory tests.

Study Intervention(s)			
Intervention Name	Tafamidis free acid tablet (fasted)	Tafamidis meglumine soft gelatin capsule (fasted)	Tafamidis free acid tablet (fed)
Arm Name (group of participants receiving a specific treatment or no treatment)	Treatment A	Treatment B	Treatment C
Type	Drug	Drug	Drug
Dose Formulation	Tablets	Softgel capsules	Tablets
Unit Dose Strength(s)	12.2 mg	20 mg	12.2 mg
Dosage Level(s)	1 x tablet	1 x capsule	1 x tablet
Route of Administration	Oral	Oral	Oral
Use	Experimental	Experimental	Experimental
IMP or NIMP/AxMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor Refer to the IPM	Provided centrally by the sponsor Refer to the IPM	Provided centrally by the sponsor Refer to the IPM
Packaging and Labeling	Study intervention will be provided in bottles. Each bottle will be labeled as required per country requirement. The product will be provided as open supplies.	Study intervention will be provided in bottles. Each bottle will be labeled as required per country requirement. The product will be provided as open supplies.	Study intervention will be provided in bottles. Each bottle will be labeled as required per country requirement. The product will be provided as open supplies.
Current/Former Name(s) or Alias(es)	PF-06291826	PF-06291826 / Vyndaqel®	PF-06291826

Study Arm(s)			
Arm Title	Treatment A	Treatment B	Treatment C
Arm Type	Test - fasted	Reference - fasted	Test - fed
Arm Description	Participants will receive a single 12.2 mg	Participants will receive a single commercial 20	Participants will receive a single 12.2 mg

Study Arm(s)			
	tafamidis free acid tablet, fasted	mg tafamidis meglumine capsule	tafamidis free acid tablet, fed
Associated Intervention Labels	Tafamidis 12.2 mg tablets	Tafamidis meglumine 20 mg capsules	Tafamidis 12.2 mg tablets

Study interventions will be supplied by Pfizer as tafamidis 12.2 mg tablets and tafamidis meglumine 20 mg soft gelatin capsules.

Pivotal BE study tablets and capsules will be supplied to the CRU in multidose labeled bottles (in sufficient number to allow unopened containers to be kept as retains).

6.1.1. Administration

On Day 1 of each period each participant will receive either tafamidis 12.2 mg tablet under fasting (Treatment A) or fed (Treatment C) conditions or tafamidis meglumine 20 mg soft gelatin capsule (Treatment B) under fasting conditions.

Following an overnight fast of at least 10 hours, participants will receive study intervention at approximately 0800 hours (plus or minus 2 hours). Participants being administered the investigational product in the fed state should start a high-fat/high-calorie breakfast (as per the description in Section 5.3.1) approximately 30 minutes prior to administration of the treatment. The breakfast will be consumed over approximately 25 minutes and investigational product administered within approximately 5 minutes after completion of the meal. Investigator site personnel will administer study intervention during each period with ambient temperature water to a total volume of approximately 240 mL. Participants will swallow the study intervention whole, and will not manipulate or chew the study intervention prior to swallowing.

In order to standardize the conditions on PK sampling days, all participants will be required to refrain from lying down (except when required for BP, pulse rate, and ECG measurements), eating, and drinking beverages other than water during the first 4 hours after dosing.

6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm that appropriate conditions (eg, temperature) have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare, and/or administer study intervention.

3. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At

a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented upon return to business.

4. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with actions taken. The site should actively pursue options for returning the study intervention to the labeled storage conditions, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the excursion definition and information to report for each excursion will be provided to the site in the IPM.

5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

6. Study interventions should be stored in their original containers.

7. The investigator, institution, head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IPM. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

9. All pivotal BA/BE retains should be stored by the investigator site or with a third party vendor. Sample retention is the responsibility of the entity performing the BA/BE study.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IPM.

6.2.1. Preparation and Dispensing

Within this protocol, preparation refers to the investigator site activities performed to make the study intervention ready for administration or dispensing to the participant by qualified staff. Dispensing is defined as the provision of study intervention, concomitant treatments, and accompanying information by qualified staff member(s) to a healthcare provider, participant, in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

Tablets and capsules will be prepared at the CRU in the individual dosing containers by 2 operators, 1 of whom is an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist). The tablets and capsules will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the clinical site's labeling requirements.

6.3. Assignment to Study Intervention

The investigator will assign participant numbers to the participants as they are screened for the study. Pfizer will provide a randomization schedule to the investigator and, in accordance with the randomization numbers, the participant will receive the study treatment regimen assigned to the corresponding randomization number.

The investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

6.4. Blinding

This is an open-label study.

6.4.1. Blinding of Participants

Participants will be unblinded to their assigned study intervention.

6.4.2. Blinding of Site Personnel

Investigators and other site staff will be unblinded to participants' assigned study intervention.

6.4.3. Blinding of the Sponsor

Sponsor staff will be unblinded to participants' assigned study intervention.

6.5. Study Intervention Compliance

Participants will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.6. Dose Modification

As this is a single-dose study, no dose modification is permitted.

6.7. Continued Access to Study Intervention After the End of the Study

No study intervention will be provided to participants at the end of their study participation.

6.8. Treatment of Overdose

For this study, any dose of PF-06291826 greater than 20 mg tafamidis meglumine or 12.2 mg tafamidis free acid within a 24-hour time period will be considered an overdose.

There is no specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the study medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE.**
5. Obtain a blood sample for PK analysis within 1 day from the date of the last dose of study intervention if requested by the study medical monitor (determined on a case-by-case basis).

6.9. Prior and Concomitant Therapy

Use of prescription or nonprescription drugs and dietary and herbal supplements are prohibited within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. Limited use of nonprescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor. Acetaminophen/paracetamol may be used at doses of ≤1 g/day.

Females taking hormone replacement therapy may be eligible to participate in this study if they are willing to discontinue therapy at least 28 days prior to the first dose of study treatment and remain off hormonal therapy for the duration of the study.

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All participants will be questioned about concomitant treatment at each clinic visit.

Treatments taken within 28 days before the first dose of study intervention will be documented as a prior treatment. Treatments taken after the first dose of study intervention will be documented as concomitant treatments.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Since this is a single-dose study, this section is not applicable.

7.1.1. ECG Changes

If a clinically significant finding is identified (including, but not limited to, changes from baseline in QTcF after enrollment), the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.1.2. COVID-19

If a participant is diagnosed with COVID-19 during the study, it should be reported as an AE or SAE (as appropriate) and appropriate medical intervention should be provided.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at their own request. Reasons for discontinuation from the study include the following:

- Refused further follow-up
- Lost to follow-up
- Death
- Study terminated by Sponsor

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The early discontinuation visit applies only to participants who are enrolled/randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

If a participant withdraws from the study, they may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations will be performed and no additional data will be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with them or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study;
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and Baseline Procedures

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to

record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Participants will be screened within 28 days prior to administration of the study intervention to confirm that they meet the study population criteria for the study. If the time between screening and dosing exceeds 28 days as a result of unexpected delays (eg, delayed drug shipment), then participants do not require rescreening if the laboratory results obtained prior to first dose administration meet eligibility criteria.

A participant who qualified for this protocol but did not enroll from an earlier cohort/group may be used in a subsequent cohort/group without rescreening, provided laboratory results obtained prior to the first dose administration meet eligibility criteria for this study. In addition, other clinical assessments or specimen collections, eg, retained research samples, may be used without repeat collection, as appropriate.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that they have taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

If an IV catheter is utilized for blood sample collections, ECGs and vital sign assessments (pulse rate and BP) should be collected prior to the insertion of the catheter.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately 228 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days.

To prepare for study participation, participants will be instructed on the information in the Lifestyle Considerations and Prior and Concomitant Therapy sections of the protocol.

8.2. Efficacy Assessments

Analysis of efficacy is not applicable to this study.

CCI [redacted]

CCI

[redacted]

CCI
CCI

[redacted]

8.3.5. COVID-19 Specific Assessments

Participants will be tested for COVID-19 infection per local site procedures prior to being admitted to the clinic for confinement and a subsequent COVID-19 test will be performed after 4 days (ie, upon completion of 4 × 24 hours in house), or if they develop COVID-19-like symptoms. Additional testing may be required by local regulations or by the PI.

CCI

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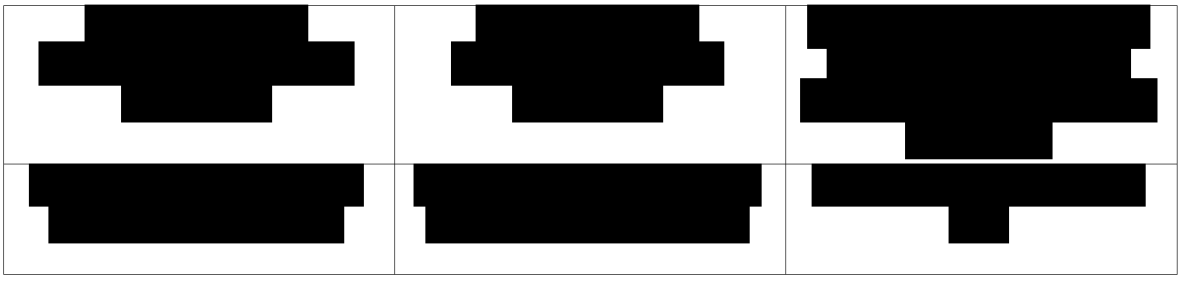

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[redacted]

[redacted]

[redacted]

8.5. Pharmacokinetics

8.5.1. Plasma for Analysis of Tafamidis

Blood samples of approximately 4 mL, to provide approximately 1.5 mL, will be collected for measurement of plasma concentrations of tafamidis as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples up to and including 10 hours after dose administration that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60-minute sample) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF/DCT. Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF/DCT. This protocol deviation window does not apply to samples to be collected more than 10 hours after dose administration at outpatient/follow-up visits with visit windows.

CCI [redacted]

Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

Samples collected for measurement of plasma concentrations of tafamidis will be analyzed using a validated analytical method in compliance with applicable SOPs.

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

8.6. Genetics

8.6.1. Specified Genetics

Specified genetic analyses are not evaluated in this study.

CCI [redacted]

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.7.1. Specified Gene Expression (RNA) Research

Specified gene expression (RNA) research is not included in this study.

8.7.2. Specified Protein Research

Specified protein research is not included in this study.

8.7.3. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.8. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.9. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in the SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Statistical Hypotheses

The alternative hypothesis of bioequivalence (H1: $q_L \leq m_T - m_R \leq q_U$), 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: $q_L \leq m_T - m_R$

HoB: $m_T - m_R > q_U$

H1B: $m_T - m_R \leq q_U$

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%).

9.2. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

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.

Participant Analysis Set	Description
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.
CCI [redacted]	[redacted]

9.3. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.3.1. Pharmacokinetic Analyses

9.3.1.1. Derivation of Pharmacokinetic Parameters

Plasma PK parameters for tafamidis will be derived (as data permit) from the concentration-time data using standard noncompartmental methods as outlined in Table 4. Actual PK sampling times will be used in the derivation of PK parameters. In the case that actual PK sampling times are not available, nominal PK sampling time will be used in the derivation of PK parameters.

Table 4. 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 from the log-linear regression analysis $C_{last}* = C_{last} \times e^{(-KEL \times Tlast)}$
CCI [redacted]	[redacted]	[redacted]

Table 4. Plasma Tafamidis Pharmacokinetic Parameters Definitions

Parameter	Definition	Method of Determination
CCI	[redacted]	[redacted]
C_{max}	Maximum observed concentration	Observed directly from data
CCI	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

*if data permit

9.3.2 Statistical Methods for PK Data

For assessment of the bioequivalence objective of the study (Periods 1 and 2), natural log transformed AUC_{inf}, AUC_{last}, CCI 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 between 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}, CCI 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.

CCI [redacted]

The plasma concentrations for tafamidis will be listed and summarized descriptively by nominal PK sampling time and treatment. Individual participant as well as mean and median profiles of the plasma concentration time data will be plotted by treatment using actual (for individual) and nominal (for mean and median) times respectively. Mean and median profiles will be presented on both linear and semi-log scales.

For summary statistics and median plots by sampling time, the nominal PK sampling time will be used. For individual participant plots by time, the actual PK sampling time will be used.

Additional specifications about the tables, listings, and figures will be outlined in the SAP.

9.3.2. Safety Analyses

All safety analyses will be performed on the safety population.

AEs, ECGs, BP, pulse rate, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG, BP, and pulse rate abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination and neurological examination information, as applicable, collected during the course of the study, will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

CCI [redacted]

9.4. Interim Analyses

No 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 and/or supporting clinical development.

9.5. Sample Size Determination

The sample size of 22 participants (11 participants per sequence in the fasted arms) to ensure a minimum of 18 PK evaluable participants for this 3-way crossover will provide 97% power that the 90% confidence interval for the ratio of Test to Reference for AUC_{inf} will lie within the acceptance region of (80%, 125%) and 89% power that 90% confidence interval for the ratio of Test to Reference treatment for C_{max} will lie within the acceptance region of (80%, 125%). Consequently, this study has approximately 86% power overall to demonstrate bioequivalence of the Test treatment to the Reference treatment [ie, equivalence in both AUC_{inf} and C_{max}]. This estimate is based on the assumption that the true ratio between Test and Reference treatments for both AUC_{inf} and C_{max} is 0.9.

The power calculations assumed the estimates of within participant standard deviations of 0.098 and 0.119 for $\log_e AUC_{inf}$ and $\log_e C_{max}$, respectively, obtained as an average from studies B3461030, B3461044 and B3461095.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, submitted to an IRB/EC by the investigator, and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of the ICH GCP guidelines that the investigator becomes aware of.

10.1.2. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about their right to access and correct their personal data and to withdraw consent for the processing of their personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

A copy of the ICD(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICD.

10.1.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to their actual identity and medical record ID. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains standard operating procedures on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

10.1.4. Committees Structure

Not applicable.

10.1.4.1. Data Monitoring Committee

This study will not use an E-DMC.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT/CTIS, and/or www.pfizer.com, and other public registries and websites in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT/CTIS

Pfizer posts clinical trial results on EudraCT/CTIS for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 24 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password-protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the data management plan [and monitoring plan] maintained and utilized by the sponsor or designee.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant’s medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and its origin can be found in the Source Document Locator, which is maintained by the sponsor.

Description of the use of the computerized system is documented in the Data Management Plan, which is maintained by the sponsor.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP guidelines, and all applicable regulatory requirements.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the CRO if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or the ICH GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.9. Publication Policy

For multicenter trials, the primary publication will be a joint publication developed by the investigator and Pfizer reporting the primary endpoint(s) of the study covering all study sites. The investigator agrees to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study-intervention or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication.

10.1.10. Sponsor's Medically Qualified Individual

The contact information for the sponsor's MQI for the study is documented in the study contact list located in the CTMS.

To facilitate access to their investigator and the sponsor's MQI for study-related medical questions or problems from nonstudy healthcare professionals, participants are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) Pfizer Call Center number.

The ECC is intended to augment, not replace, the established communication pathways between the participant and their investigator and site staff, and between the investigator and sponsor study team. The ECC is only to be used by healthcare professionals not involved in the research study, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number is to be used when the investigator and site staff are unavailable. The Pfizer Call Center number is not for use by the participant directly; if a participant calls that number directly, they will be directed back to the investigator site.

CCI

[redacted]

[redacted]

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms;
 	
  • Requires additional diagnostic testing or medical/surgical intervention;
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition, including an increase in either frequency and/or intensity of the condition.
 	
• New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic

The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording/Reporting and Follow-Up of AEs and/or SAEs During the Active Collection Period

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs on the CT SAE Report Form to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding	All AEs/SAEs associated with EDP or EDB **Note:** Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE)**
Environmental or occupational exposure to the product under study to a nonparticipant (not involving EDP or EDB)	None. Exposure to a study non-participant is not collected on the CRF	The exposure (whether or not there is an associated AE or SAE) must be reported***

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the CT SAE Report Form.

** **EDB** is reported to Pfizer Safety using the CT SAE Report Form, which would also include details of any SAE that might be associated with the EDB.

*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the CT SAE Report Form.

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE or SAE CRF page.

- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual ADL.

- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual ADL, causing discomfort, but poses no significant or permanent risk of harm to the research participant.

- Severe: A type of AE that interrupts usual ADL, or significantly affects clinical status, or may require intensive therapeutic intervention.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

- The investigator will also consult the IB and/or product information, for marketed products, in their assessment.

- For each AE or SAE, the investigator **must** document in the medical notes that they have reviewed the AE or SAE and have provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor**.

- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-Up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings, including histopathology.

- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via the CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

No contraception methods are required for male participants in this study, as the calculated safety margin is ≥100-fold between the estimated maternal exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies.

10.4.2. Female Participant Reproductive Inclusion Criteria

The criterion below is part of Inclusion Criterion 1 (Age and Sex; Section 5.1) and specify the reproductive requirements for including female participants.

A female participant is eligible to participate if she is not pregnant or breastfeeding and the following condition applies:

- Is not a WOCBP

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

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10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-Up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are "adaptors" or are "susceptible."

In the majority of DILI cases, elevations in AST and/or ALT precede T bili elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to T bili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and T bili baseline values within the normal range who subsequently present with AST OR ALT values ≥3 × ULN AND a T bili value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** T bili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values AND ≥3 × ULN; or ≥8 × ULN (whichever is smaller).

    - Preexisting values of T bili above the normal range: T bili level increased from baseline value by an amount of ≥1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

Rises in AST/ALT and T bili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and T bili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and T bili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.7. Appendix 7: Kidney Safety: Monitoring Guidelines

10.7.1. Laboratory Assessment of Change in Kidney Function and Detection of Kidney Injury

Standard kidney safety monitoring requires assessment of baseline and postbaseline serum creatinine Scr-based eGFR or eCrCl). Baseline and postbaseline serum Scys makes it feasible to distinguish AKI from other causes of Scr increase. If Scr increase is confirmed after baseline, then reflex measurement of Scys is indicated to estimate the combined Scr-Scys eGFR calculation (for adults only).

Regardless of whether kidney function monitoring tests are required as a routine safety monitoring procedure in the study, if the investigator or sponsor deems it necessary to further assess kidney safety and quantify kidney function, then these test results should be managed and followed per standard of care.

10.7.2. Age-Specific Kidney Function Calculation Recommendations

10.7.2.1. Adults (18 Years and Above)—2021 CKD-EPI Equations

2021 CKD-EPI Scr Only	**Scr** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ≤ 0.7	N/A	$eGFR = 143 \times (Scr/0.7)^{-0.241} \times (0.9938)^{Age}$
Female	if > 0.7	N/A	$eGFR = 143 \times (Scr/0.7)^{-1.200} \times (0.9938)^{Age}$
Male	if ≤ 0.9	N/A	$eGFR = 142 \times (Scr/0.9)^{-0.302} \times (0.9938)^{Age}$
Male	if > 0.9	N/A	$eGFR = 142 \times (Scr/0.9)^{-1.200} \times (0.9938)^{Age}$
2021 CKD-EPI Scr-Scys Combined	**Scr** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ≤ 0.7	if ≤ 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if ≤ 0.7	if > 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Female	if > 0.7	if ≤ 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if > 0.7	if > 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if ≤ 0.9	if ≤ 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if ≤ 0.9	if > 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if > 0.9	if ≤ 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if > 0.9	if > 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$

Inker LA et al. N Engl J Med. 2021;385:1737-49.

10.7.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

AE grading for decline in kidney function (ie, eGFR or eCrCl) will be according to KDIGO criteria.

10.8. Appendix 8: ECG Findings of Potential Clinical Concern

ECG Findings That May Qualify as AEs

- Marked sinus bradycardia (rate <40 bpm) lasting minutes.
- New PR interval prolongation >280 ms.
- New prolongation of QTcF to >480 ms (absolute) or by ≥60 ms from baseline.
- New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm.
- New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration.
- Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.

ECG Findings That May Qualify as SAEs

- QTcF prolongation >500 ms.
- New ST-T changes suggestive of myocardial ischemia.
- New-onset LBBB (QRS complex>120 ms).
- New-onset right bundle branch block (QRS complex>120 ms).
- Symptomatic bradycardia.
- Asystole:
  - In awake, symptom-free participants in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node.
  - In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer.
  - Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
- Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (HR <40 bpm), accelerated idioventricular rhythm (HR >40 bpm to <100 bpm), and

monomorphic/polymorphic ventricular tachycardia (HR >100 bpm [such as torsades de pointes]).

- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all-inclusive of what to be reported as AEs/SAEs.

10.9. Appendix 9: Prohibited Concomitant Medications That May Result in DDI

Not applicable to this study.

10.10. Appendix 10: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
A1 to A3	albuminuria (KDIGO albuminuria severity standardization)
Abs	absolute
ADL	activity/activities of daily living
AE	adverse event
AKI	acute kidney injury
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATTR-CM	transthyretin cardiomyopathy
ATTR-PN	transthyretin polyneuropathy
AUC	area under the concentration-time curve
AUC_{72}	area under the concentration-time curve from time 0 to 72 hours
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
AV	atrioventricular
AxMP	auxiliary medicinal product
β-hCG	β-human chorionic gonadotropin
BA	bioavailability
BBS	Biospecimen Banking System
BE	bioequivalence
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology
C_{max}	maximum observed concentration
CMC	Chemistry, Manufacturing and Controls
CO_2	carbon dioxide (bicarbonate)
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	Clinical Study Report
CT	clinical trial

Abbreviation	Term
CTMS	clinical trial management system
CTIS	Clinical Trial Information System
CV	cardiovascular
DCT	data collection tool
DDI	drug-drug interaction
DILI	drug-induced liver injury
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram or electrocardiography
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
E-DMC	External Data Monitoring Committee
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clincal Trials (European Clinical Trials Database)
FDA	US Food and Drug Administration
FIH	First-in-human
FSH	follicle-stimulating hormone
F/U	follow-up
G1 to G5	Grade (KDIGO eGFR category standardization)
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HR	heart rate
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IPAL	Investigational Product Accountability Log
IPM	investigational product manual
IRB	Institutional Review Board

Abbreviation	Term
IV	intravenous(ly)
KDIGO	Kidney Disease Improving Global Outcomes
k_{el}	first-order elimination rate constant
LBBB	left bundle branch block
LDL	low-density lipoprotein
LFT	liver function test
log_e	natural logarithm
MQI	medically qualified individual
CCI	[redacted]
N/A	Not Applicable
NIMP	noninvestigational medicinal product
NOAEL	no observed adverse effect level
PD	pharmacodynamic(s)
PE	physical examination
PI	Principal Investigator
PK	pharmacokinetic(s)
PT	prothrombin time
PVC	premature ventricular contraction
QD	once daily
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
qual	qualitative
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
Scr	serum creatinine
Scys	serum cystatin C
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single-reference safety document
SUSAR	Suspected Unexpected Serious Adverse Reaction
CCI	[redacted]
T bili	total bilirubin
THC	tetrahydrocannabinol
CCI	[redacted]
ULN	upper limit of normal
US	United States
UTI	urinary tract infection
WBC	white blood cell
WOCBP	woman/women of childbearing potential

11. REFERENCES

[i] Investigator's Brochure, B346 (PF-06291826) 19 Mar 2021