FOLDRX PHARMACEUTICALS, A PFIZER COMPANY

A MULTICENTER, INTERNATIONAL, PHASE 3, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED STUDY TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF DAILY ORAL DOSING OF TAFAMIDIS MEGLUMINE (PF-06291826) 20 MG OR 80 MG IN COMPARISON TO PLACEBO IN SUBJECTS DIAGNOSED WITH TRANSTHYRETIN CARDIOMYOPATHY (TTR-CM)

Compound:	PF-06291826
Compound Name:	tafamidis
US IND Number:	IND 71,880
European Clinical Trial Database (EudraCT) Number:	2012-002465-35
Protocol Number:	B3461028
Phase:	3

[redacted]

Document History

Document	Version Date	Summary of Changes
Original protocol	31 Jul 2013	N/A
Amendment 1	16 Apr 2014	Following initiation of the study the following changes were made to the study protocol: 1. Typographical corrections and clarifications. 2. Added the results of the B3461031 study indicating a lack of tafamidis effect on QTc. 3. Clarified the target sample size as 400 subjects. 4. Added "Smoking and Alcohol Classification" to the Schedule of Activities. 5. Removed Serum Amyloid A from required Screening analysis as it is an indicator of an active inflammatory process and does not contribute to defining an appropriate subject for this study. 6. Amended the Week 2 follow-up to allow for flexibility in scheduling a visit to either the investigator's clinic or their primary care physician's office or a visit to a local laboratory for blood collection (which would also include, a phone call). 7. The second 6MWT during Screening was removed in order to ease the burden of site visits. 8. Removed chest x-ray as a required Screening test. 9. Clarified the duration of a Screening extension as being 2 weeks. 10. Clarified language for eligibility requirements for the extension study that include completion of at least 896 days in this study. 11. Change to provide additional diagnostic evaluations via IHC and scintigraphy to support diagnosis of TTR-CM.

		12. Added procedures for confirming TTR cardiomyopathy in TTR genotype positive subjects with elevated kappa and lambda light chain values. 13. Removed the 5 year limitation on biopsies for TTR determination. 14. Added examples of calcium channel blockers that should be excluded from use in this study (eg verapamil, diltiazem). 15. Updated the method of determining glomerular filtration. 16. Added tauroursodeoxycholate and doxycycline to the list of excluded medications. 17. Added that the discontinuation of NSAIDs must be 30 days before the Baseline visit. 18. Expanded 30 month Vital Status determination to include Transplant Status. 19. Added diflunisal assay. 20. Changed exclusion language for "prior myocardial infarction" to exclude subjects who in the opinion of the investigator do not have heart failure caused by TTR cardiomyopathy. 21. Added 30 day exclusion for use of tauroursodeoxycholate and doxycycline prior to enrollment and their exclusion from use during the study. 22. Clarified that all follow-up visits need to be referenced to the date of the Baseline visit and that the anticipated study duration is 910 days. 23. Added language clarifying the term "down-titration". 24. Removed the Endocrine, Immunologic / Allergic, and Hematologic / Lymphatic systems from the Screening physical examination because they had been entered in error.

		25. Entered echocardiographic parameters for the assessment of Longitudinal, Circumferential and Radial Echo Strain. 26. Clarified that coagulation variables will be measured in the local laboratory. 27. Removed the "Total Blood Volumes " chart and indicated the central lab manual as the source of the blood volumes at each visit. 28. Removed the 15 month time frame from the enrollment period. 29. Clarified the wording for "censoring" of subjects in the statistical section. 30. Added supportive references, 31. Removed the "6 Minute Walk Test Worksheet" as it doesn't match the eCRF. 32. Replaced "appointment card" with "Subject Daily Dosing Diary". 33. Replaced "study medication card" and "blister pack" with "study medication wallet". 34. Added TTR oligomer concentration as an exploratory endpoint. 35. Needed to add and rearrange language because of a company global change to the protocol template.
Amendment 2	26 Feb 2015	1. Added contraception discussion to schedule of activities, as described in the protocol (section 4.3.1). 2. Added subjects who undergo surgery for Implantation of a cardiac mechanical assist device will be treated in the analysis similarly to subjects receiving a heart transplant. 3. Added conversion of NT proBNP to SI units. 4. Added clarification for Hepatitis and HIV exclusion.

		5. Added clarifying text to Contraindicated Therapies (section 5.8.1). 6. Added language to comply with the new Pfizer protocol template (Endpoint Adjudication and Communication of Results by Pfizer).
Amendment 3	24 May 2016	1. Clarified the term "down-titration" to "dose reduction" to more accurately represent the change in dose that may occur when a subject is unable to tolerate the randomized dose. 2. Removed reference to the color of the capsules under 'Appearance' in tabular summary of the investigational product (active and matching placebo), to eliminate confusion with a change in *investigational product manufacture* (implemented in protocol administrative change letter dated 11 Apr 2016). 3. Added the collection of urine samples at Months 12, 18, 24, and 30 or (Early Study Discontinuation) to be used in assay development for measurement of TTR oligomer concentrations in urine to be performed at selected centers. 4. Added the collection of blood samples for testing of tafamidis concentrations in subjects who require dialysis or hemofiltration after randomization and while on study treatment. 5. Removed the requirement for blood samples at Months 12 and 24 for testing of diflunisal concentrations. 6. Clarified that subjects who do not enroll in the extension study will be followed for 28 calendar days after the last dose of study medication for collection of adverse events. Subjects who enroll in the extension study will continue to be monitored for adverse events within the extension study. 7. Clarified that the Endpoint Adjudication Committee (EAC) Guidelines have been incorporated into the updated EAC Charter. 8. Better delineated the analysis planned for Kansas City Cardiomyopathy Questionnaire (KCCQ) scores related to subject symptoms.

		9. Incorporated the discontinuation of enrollment of subjects with wild-type genotype in order to increase the numbers of subjects with variant genotype (implemented in protocol administrative change letter dated 30 Jun 2015). 10. Provided the study number for the extension study and clarified that all subjects in the extension study will receive tafamidis; however, the dose will be blinded in order to maintain blinding in the B3461028 study. 11. Clarified that dosing is permitted in the PM when the timing of pharmacokinetic samples is prohibitive for adherence with AM dosing. 12. Added the requirement that urine should be sent for microscopic evaluation following any positive test on urine dipstick, not just a positive test for blood or protein. 13. Removed inconsistent information found in Section 7.8 Hospitalization Determination on the follow-up required for Month 30 vital status / transplant / cardiac mechanical assist device to reflect what is being collected. Follow-up at Month 30 for this information is still included in Section 6.3 Subject Withdrawal and Vital Status / Transplant / Cardiac Mechanical Assist Device Status Follow-up. 14. Clarified that events resulting in organ transplantation or cardiac mechanical assist device should be considered "medically important" and, therefore, reported as serious adverse events. 15. Redefined the baseline groupings for New York Heart Association (NYHA) Functional Classification that will be used for efficacy analyses, grouping subjects with NYHA Class I and II together to be compared against NYHA Class III 16. Amended the description and frequency of data review by the External Data Monitoring Committee (E-DMC) to be consistent with the E-DMC charter.

		17. Added or revised language to comply with the updated Pfizer protocol template (Section 4.3.1 Contraception, Section 5.6 Drug Storage, Section 5.7.1 Destruction of Investigational Product Supplies, Section 10 Quality Control and Quality Assurance, Section 12.3 Subject Information and Consent). 18. Deleted Section 12.4 Subject Recruitment as this language is now included in revised Pfizer protocol template language under Section 12.3 Subject Information and Consent. 19. Several typographical and formatting errors were corrected.

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

This is a list of abbreviations	
Abbreviation	**Term**
6MWT	6 Minute Walk Test
99mTC-DPD	Technetium-99m-3,3-diphosphono-1,2-propano-dicarboxylic acid
99mTC- PYP	Technetium-99m - Pyrophosphate
99mTC-HMDP	Technetium-99m - hydroxymethylene diphosphonate
AE	adverse event
AL	immunoglobulin light chain amyloidosis
ALT	alanine transaminase
ANOVA	analysis of variance
anti-HCV	Serology for hepatitis C
AST	aspartate transaminase
AV	atrioventricular
BUN	blood urea nitrogen
CDS	core data sheet
C_{max}	Maximum drug concentration
$C_{max,ss}$	Maximum drug concentration at steady state
CMH	Cochran-Mantel-Haenszel
$C_{min,ss}$	Minimum drug concentration at steady state
CRF	case report form
CSA	clinical study agreement
CTA	clinical trial application
DNA	deoxyribonucleic acid
EAC	Endpoint Adjudication Committee
EC	ethics committee
ECG	electrocardiogram
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EDTA	edetic acid (ethylenediaminetetraacetic acid)
EQ-5D-3L	EuroQoL-5 Dimensions
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FAPWTR	Familial Amyloidotic Polyneuropathy World Transplant Registry
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act of 2007 (United States)
free Hb	Free hemoglobin
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate

HBsAg	serology for hepatitis B
hCG	human chorionic gonadotropin
HF	Heart Failure
HIV	human immunodeficiency virus
IB	investigator's brochure
ICD	informed consent document
ICH	International Conference on Harmonisation
ID	identification
IHC	immunohistochemistry
IND	investigational new drug application
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
IUD	intrauterine device
KCCQ-OS	Kansas City Cardiomyopathy Questionnaire – Overall Summary
LFT	liver function test
LSLV	last subject last visit
LV	left ventricle
mBMI	modified Body Mass Index
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MGUS	monoclonal gammopathy of undetermined significance
MHLW	Ministry of Health, Labor and Welfare
MMRM	mixed model repeated measures ANCOVA
MR	molar ratio of tafamidis:TTR plasma concentration
MRI	magnetic resonance imaging
N/A	not applicable
NSAID	Non-Steroidal Anti-Inflammatory Drug
NT-proBNP	N-Terminal prohormone B-type Natriuretic Peptide (NT-proBNP)
NYHA	New York Heart Association
PA	posterior-anterior
PGA	Patient Global Assessment
PK	Pharmacokinetic
PK/PD	Pharmacokinetic/Pharmacodynamic
PP	per protocol
PR	PR interval on the ECG
PT	prothrombin time
QD	once daily dosing
QRS	QRS duration on the ECG
QT	QT duration on the ECG

QTc	Corrected ECG QT Interval
QTc (B and F)	Corrected ECG QT Interval using the Bazett's or Fridericia's correction
RNA	ribonucleic acid
RR	RR interval on the ECG
SA	sinoatrial
SAE	serious adverse event
SAP	statistical analysis plan
SI units	Standard International units
SOP	standard operating procedure
SRSD	single reference safety document
TEAE	Treatment Emergent Adverse Events
TRACS	Transthyretin Amyloid Cardiac Study
TTR	Transthyretin
TTR-CM	Transthyretin Cardiomyopathy
TTR-FAP	Transthyretin Familial Amyloid Polyneuropathy
ULN	upper limit of normal
US	United States
USPI	United States package insert
UTN	Universal Trial Number

PROTOCOL SUMMARY

Background and Rationale:

Transthyretin amyloid disease is a rare and fatal condition characterized by the deposition of amyloid derived from transthyretin (a plasma protein) in various organs and tissues. Deposition of TTR amyloid is associated with two distinct clinical presentations: transthyretin familial amyloid polyneuropathy (TTR-FAP) when the peripheral nerves are primarily affected and transthyretin amyloid cardiomyopathy (TTR-CM) when the heart is primarily affected. Both TTR-FAP and TTR-CM are associated with genetic variants of transthyretin but TTR-CM may also occur in the absence of any genetic mutation and may be due to wild-type TTR amyloid deposition. At this time, with the exception of the approval of tafamidis for TTR-FAP in the European Union (EU) and Japan, there are no approved pharmacotherapies for these conditions.

TTR-CM occurs when TTR amyloid fibrils infiltrate the myocardium, leading to deposits of extracellular amyloid. Deposition of transthyretin fibrils occurs between the myocardial cells and produces a thickening and stiffening of the myocardial tissue. This infiltration of the myocardium results in diastolic dysfunction progressing to restrictive cardiomyopathy, congestive heart failure, and ultimately death.

Pfizer is developing tafamidis, an oral small molecule, for the treatment of transthyretin amyloid diseases. It has been demonstrated to bind selectively to TTR in human blood and slow fibril formation in vitro (Razavi 2003).[40] It binds to the 2 thyroxine binding sites with negative cooperativity, exhibiting dissociation constants of 2 nM [Kd1] and 154 nM [Kd2] (DeVit 2006)[11] and kinetically stabilizing the TTR tetramer when bound (Sekijima 2009).[46]

TTR stabilization has been hypothesized to lead to slowing or halting of disease progression. This hypothesis was confirmed in a double-blind, placebo-controlled, 18-month study in subjects with TTR-FAP, in which those subjects receiving tafamidis had better neurologic outcomes compared with those receiving placebo. In order to improve the understanding of the natural history of TTR-CM, a longitudinal, observational clinical study of 29 subjects with either the V122I genetic variant (11 subjects) or wild-type (18 subjects) associated TTR-CM (Transthyretin Amyloid Cardiac Study; TRACS) was undertaken. A follow-up Phase 2 open-label interventional study (Study Fx1B-201) demonstrated TTR stabilization in subjects with V122I and wild-type TTR-CM and an acceptable safety profile following 12 months of tafamidis 20 mg given once daily.

Study B3461031 was designed to evaluate the effect of tafamidis on the corrected QT (QTc) interval in healthy volunteers. The primary objective was to characterize the effect of a supra-therapeutic tafamidis concentration (~20 µg/mL) on the QTc interval relative to placebo in healthy volunteers. A supra-therapeutic, single, 400 mg oral-dose of tafamidis solution in healthy volunteers demonstrated a lack of an effect on QTc interval prolongation. Single doses of moxifloxacin 400 mg established that the study had adequate sensitivity to detect increases in the QTc interval.

Objectives and Endpoints:

The objective of this study is to determine the efficacy, safety, and tolerability of tafamidis in subjects with transthyretin cardiomyopathy

The primary objective is to assess the efficacy, safety, and tolerability of an oral dose of 20 mg or 80 mg tafamidis meglumine soft gel capsules in comparison to placebo and given once daily, in addition to standard of care, for 30 months in subjects diagnosed with either a TTR variant or wild-type TTR-CM. The study is designed to assess the potential for benefit from treatment with tafamidis relative to placebo based on all-cause mortality and frequency of cardiovascular-related hospitalizations (including heart failure, arrhythmia, myocardial infarction, and stroke as well as other cardiovascular-related events).

Primary Analysis:

The primary analysis uses a hierarchical combination applying the method of Finkelstein-Schoenfeld (Finkelstein 1999)[16] to all-cause mortality and frequency of cardiovascular-related hospitalizations, which is defined as the number of times a subject is hospitalized (ie, admitted to a hospital) for cardiovascular-related morbidity.

Secondary Endpoints:

Analysis of the following key secondary endpoints will follow an alpha conserving strategy:

1. Change from Baseline to Month 30 on the distance walked during the 6-Minute Walk Test (6MWT) (Appendix 4).

2. Change from Baseline to Month 30 on the Kansas City Cardiomyopathy Questionnaire Overall Summary score (KCCQ-OS) (Appendix 1.1).

The following additional secondary endpoints will be analyzed without an alpha conserving strategy for multiple comparisons:

1. Cardiovascular-related mortality,

2. Frequency of cardiovascular-related hospitalization,

3. All-cause mortality,

4. TTR Stabilization at Month 1.

Study Design:

This is an international, multicenter, double-blind, placebo-controlled, randomized, 3-arm study with a 30-month treatment phase wherein subjects with transthyretin cardiomyopathy, due to either variant or wild-type TTR, will receive either 20 mg (n= 80) or 80 mg (n = 160) tafamidis or matching placebo (n = 160) once daily, in addition to standard of care. The

study includes a provision for sites to implement a blinded dose reduction to 40 mg once daily for subjects who experience adverse events that may be associated with the tolerability of treatment with tafamidis.

Selection of Subjects:

Subjects that will be included into the protocol must meet specific inclusion criteria that include but is not limited to the following:

1. A medical history of Heart Failure (HF) with at least 1 prior hospitalization for HF or clinical evidence of HF (without hospitalization) manifested by signs or symptoms of volume overload or elevated intracardiac pressures (eg, elevated jugular venous pressure, shortness of breath or signs of pulmonary congestion on x-ray or auscultation, peripheral edema) that required/requires treatment with a diuretic for improvement.

2. Evidence of cardiac amyloid by echocardiography with an end-diastolic interventricular septal wall thickness > 12 mm.

3. Presence of amyloid deposits in biopsy tissue and TTR precursor protein identification by mass spectrometry, immunohistochemistry or scintigraphy.

4. An NT-proBNP concentration $\geq$ 600 pg/mL.

5. A 6-Minute Walk Test distance > 100 meters.

Subjects will be excluded if they have:

1. A New York Heart Association (NYHA) classification of IV.

2. Glomerular filtration rate (eGFR) of < 25 mL/min./1.73 m2.

3. Use of certain non-steroidal anti-inflammatory drugs (NSAIDs), see Section 5.8.1.

4. Modified Body Mass Index (mBMI) below 600.

Study Treatment:

Investigators will confirm the eligibility of each subject to meet inclusion/exclusion criteria. An Interactive Response Technology (IRT) system will assign a unique subject identification number sequentially to each subject who has signed the informed consent document (ICD). This identifying number will be retained throughout the duration of study participation.

Subject eligibility for participation in the treatment phase of the protocol will be determined following the assessments at the Screening and Baseline visits. Subjects will be screened for eligibility and those who meet the inclusion criteria and do not meet the exclusion criteria, will be randomized. There will be a treatment assignment stratification by TTR genotype

(variant or wild-type) as well as by Baseline severity (NYHA Class I and NYHA Classes II and III combined). Subjects will receive either 20 mg (n= 80) or 80 mg (n = 160) tafamidis or matching placebo (n = 160) once daily, in addition to standard of care (eg, diuretics) for 30 months. Tafamidis is available in 20 mg soft gel capsules, and subjects will take 4 capsules per day of blinded therapy. The study includes a provision for sites to implement a blinded dose reduction to 40 mg once daily for subjects who experience adverse events that may be associated with the tolerability of treatment with tafamidis.

Dosage Level	**Compound**	**Appearance**	**Number of Capsules Per Day (Dose)**
Tafamidis meglumine 20 mg	PF-06291826	Oblong soft gelatin capsules	1 (Tafamidis 20 mg capsule) 3 (Placebo capsules)
Tafamidis meglumine 40 mg (in the event of blinded dose reduction for the 80 mg dose)	PF-06291826	Oblong soft gelatin capsules	2 (Tafamidis 20 mg capsules) 2 (Placebo capsules)
Tafamidis meglumine 80 mg	PF-06291826	Oblong soft gelatin capsules	4 (Tafamidis 20 mg capsules)
Placebo for Tafamidis		Oblong soft gelatin capsules	4 (Placebo capsules)

The study will use an External Data Monitoring Committee (E-DMC) that will be responsible for ongoing monitoring of the safety of subjects in the study according to the E-DMC Charter.

Statistical Method:

Sample Size

The target sample size is 400 subjects. Sample size estimation assumptions include an all-cause mortality rate of 12.5% for the tafamidis group and 25% for the placebo group and 1.5 cardiovascular-related hospitalizations for the tafamidis group and 2.5 cardiovascular-related hospitalizations for the placebo group (Connors 2011).[9] With a treatment duration of 30 months and a significance level (alpha) of 0.05 (two-sided test), a sample size of 300 (n=120 for placebo, n=60 for 20 mg, and n=120 for 80 mg) yields a power over 90% (for the primary comparison), which assumes pooling of the tafamidis 20 mg and 80 mg dose groups. An alternative assumption of 30% reduction in mortality (17.5 % for tafamidis and 25% for placebo) yields a power of approximately 80%. Sample size estimation was performed based on simulations, given that no closed-form sample size estimation solution is available for the primary analysis method.

In this rare disease area, prior information on treatment response is limited. A sample size of 300 subjects would provide over 90% power with 50% treatment effect (reduction in mortality). That assumption is based on open-label, uncontrolled data with tafamidis and represents a large effect in the area of cardiovascular studies. Based on the uncertainty of the assumptions due to limited data, the target sample size is 400 subjects (n=160 for placebo, n=80 for 20 mg, and n=160 for 80 mg).

Analysis Populations

The intent-to-treat (ITT) analysis set will include all subjects in the safety population who had at least 1 post-Baseline efficacy evaluation (ie, post-Baseline hospitalization, study visit, or date of death). The per protocol (PP) analysis set will include all subjects in the ITT set who did not violate any inclusion/exclusion criteria and who did not have protocol violations considered to impact the interpretation of the primary efficacy analysis. The safety analysis set will include all subjects who are enrolled (randomized) and received at least 1 dose of double-blind medication.

Primary Efficacy Analysis

The primary analysis will be based on the ITT analysis set and will combine the subjects in the tafamidis 20 mg and tafamidis 80 mg groups (including subjects in the 80 mg group that may have had a dose reduction to 40 mg) into one pooled group. This pooled group (tafamidis) will be compared with the placebo group using the Finkelstein-Schoenfeld method. The test is based on the principle that each subject in the clinical study is compared to every other subject within strata in a pair-wise hierarchical fashion using all-cause mortality first, assigning a +1 to the “better” subject and a -1 to the “worse” subject. The stratified test statistic is based on the sum of these scores within strata. The null hypothesis for the primary analysis is that neither all-cause mortality nor frequency of cardiovascular-related hospitalizations is different between the tafamidis and placebo treatment groups. The corresponding alternative hypothesis is that at least one and possibly both all-cause mortality and frequency of cardiovascular-related hospitalizations are different between the tafamidis and placebo treatment groups.

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to STUDY PROCEDURES and ASSESSMENTS sections 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 on the schedule of activities, for dispensing drug and dose reduction as well as to conduct evaluations or assessments required to protect the well-being of the subject.

Protocol Activity	**Screening Period**	**Base Line**		**Month**										
	Day -45 to Day -10	**Day 1**	**Week 2[a]**	**1**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30 (Day 910) (or Early Study Discontinuation)**
Visit Window (± weeks)			1	1	2	2	2	2	2	2	2	2	2	2
Informed Consent and Release of Medical Information Form	X													
Medical History	X	X												
Smoking and Alcohol Classification	X													
Review entrance criteria		X												
Randomization		X												
Physical examination (full)	X													X
Brief physical examination		X		X	X	X	X	X	X	X	X	X	X	
Height	X													
Weight	X	X		X	X	X	X	X	X	X	X	X	X	X
12 Lead ECG	X	X[b]		X		X		X		X		X		X
Vital signsc	X	X		X	X	X	X	X	X	X	X	X	X	X
Echocardiogram	X					X				X				X
Tissue biopsy[d]	X													
Laboratory samples														

Protocol Activity	Screening Period	Base Line		Month										
	Day -45 to Day -10	Day 1	Week 2[a]	1	3	6	9	12	15	18	21	24	27	30 (Day 910) (or Early Study Discontinuation)
Hematology	X	X	X	X		X		X		X		X		X
Serum Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation (INR, PT – Local)[e]	X	X		X		X		X		X		X		X
Retinol Binding Protein		X		X		X		X		X		X		X
Serology (HBsAg, anti-HCV, and HIV)	X													
Serum/urine test for primary (light chain) amyloidosis (AL)	X													
Urinalysis	X	X		X		X		X		X		X		X
Genotyping	X													
Pregnancy test [f]	X	X		X		X		X		X		X		X
TTR stabilization, TTR oligomer concentration, and TTR concentration[g]		X		X		X		X		X		X		X
Urine TTR oligomer concentration[h]								X		X		X		X
Tafamidis Concentrations [i]		X		X		X		X		X		X		X
Tafamidis concentrations (for subjects receiving dialysis or hemofiltration)[j]			----------Any time during the study----------											
Diflunisal concentration[k]	X	X		X		X				X				X
Pharmacogenetic sample		X												
NT – proBNP, troponin I	X	X						X						X
6MWT	X	X				X		X		X		X		X
KCCQ [l]		X				X		X		X		X		X
EQ-5D-3L[m]		X				X		X		X		X		X
PGA[n]		X				X		X		X		X		X
NYHA classification[o]	X	X				X		X		X		X		X

Protocol Activity	Screening Period	Base Line		Month										
Concomitant medications[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record time of dosing				X		X		X		X		X		X
Record dosing adherence				X	X	X	X	X	X	X	X	X	X	X
Adverse Events reporting		X	X	X	X	X	X	X	X	X	X	X	X	X[q]
Hospitalization determination		X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense blinded medication		X			X	X	X	X	X	X	X	X	X	
Documentation of vital transplant and implant status[r]		X	X	X	X	X	X	X	X	X	X	X	X	X
Contraception Discussion[s]	X	X		X	X	X	X	X	X	X	X	X	X	

a. The Week 2 "visit" will allow the subject to either come to the clinic, or consist of a telephone call to the subject for specified data determination and having the subject go to a local laboratory or local physician's office to have their needed laboratory samples collected and shipped to the central laboratory.

b. Baseline (Day 1) ECG pre-dose.

c. Systolic and diastolic blood pressure and pulse rate (supine at least 3 minutes and standing at least 2 minutes prior to assessment), respiration rate and body temperature

d. Biopsy must be performed at Screening or have been performed and documented previously.

e. INR and PT will be determined at the site's local laboratory.

f. For women of childbearing potential. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.

g. TTR stabilization, TTR oligomer concentration, and TTR concentration: Baseline (Day 1) sample: collect at any time pre-dose during the clinic visit. Month 1 sample: collect pre-dose and at 3 hours (± 1.5 hours) post-dose; Month 6 sample: collect at 7 hours (± 2.5 hours) post-dose; Month 12 sample: collect at 7 hours (± 2.5 hours) post-dose; Month 18 sample: collect at 1 hour (± 30 minutes) post-dose; Month 24 sample: collect at 1 hour (±30 minutes) post-dose; Month 30 sample: at any time during clinic visit.

h. Subjects at selected centers will provide a urine sample to be used in assay development for measurement of TTR oligomer concentrations in urine. For those subjects who provide consent, a 10 mL aliquot of urine will be collected (starting at the earliest possible prospective visit for the subject) at Months 12, 18, 24, and 30 (or Early Study Discontinuation); this aliquot will be obtained from the urine sample already collected for urinalysis at these visits.

i. Baseline (Day 1) tafamidis concentration sample: collect at any time pre-dose during the clinic visit. Month 1 tafamidis concentration sample: collect pre-dose and at 3 hours (±1.5 hours) post-dose; Month 6 tafamidis concentration sample: collect at 7 hours (± 2.5 hours) post-dose; Month 12 tafamidis concentration samples: collect at 7 hours (± 2.5 hours) post-dose; Month 18 tafamidis concentration sample: collect at 1 hour (± 30 minutes) post-dose; Month 24 tafamidis concentration sample: collect at 1 hour (± 30 minutes) post-dose; Month 30 tafamidis concentration: collect at any time during the clinic visit.

j. Should a subject require dialysis or hemofiltration at any time after randomization while on study treatment, the subject should have blood samples collected for tafamidis concentrations around the time of renal replacement therapy. The timing of the sample collection will depend on the type of renal replacement therapy administered. For hemodialysis or hemofiltration, samples should be collected on the date of the renal replacement therapy both prior to administration and after administration. When peritoneal dialysis is administered, the first sample should be collected at initiation of the first exchange. The second sample should be collected after the first exchange is completed (if performed outside of the home) or at least 24 hours after the initiation of the first exchange (if administered at home). Every effort should be made to collect these samples on the date of the subject's first administration of renal replacement therapy in the study; however, if this is not possible, the samples should be obtained as soon as possible on the date of a renal replacement therapy treatment. If necessary, the sample collection can be obtained using the guidelines for lab sample collection in the Guidance for Remotely Conducted Study Visits provided for the study. At the time of sample collection, the date and time of the last dose and the date and time of sample collection must be recorded.

k. Diflunisal concentration to determine if there is evidence of exposure to diflunisal prior to or during the study. Sample can be collected at any time during the clinic visit, after the ECG blood pressure and vital signs.

l. Kansas City Cardiomyopathy Questionnaire (KCCQ) (Appendix 1.1) should be completed before the EQ-5D-3L (Appendix 2) and PGA (Appendix 3).

m. EuroQoL-5 Dimensions (EQ-5D-3L) (Appendix 2) to be completed after the KCCQ (Appendix 1.1).

n. Patient Global Assessment (PGA) should be completed after the KCCQ (Appendix 1.1) and EQ-5D-3L (Appendix 2).

o. NYHA – New York Heart Association classification.

p. At the Screening visit, this will be Prior Medications.

q. Except for subjects who are randomized into the extension study (Study B3461045), all other subjects will have a 4-week (28 calendar days) safety follow-up visit after the last dose of the study medication for collection of adverse events. This visit can be completed by telephone.

r. When the Vital Status is determined, the subject should be asked if they have undergone a heart and/or liver transplant or implantation of cardiac mechanical assist device. This is especially important at the 30 month visit. If a subject indicates that they have had a transplant and they are still enrolled in the study, they should be removed from the study.

s. For all subjects who, in the opinion of the investigator, are biologically capable of having children and are sexually active; at each study visit, discuss with the subject the need to use highly effective contraception consistently and correctly, instruct the subject to call immediately if a selected birth control method is discontinued or if pregnancy is known or suspected and document such conversation in the patient chart.

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APPENDICES

1. INTRODUCTION

1.1. Indication

Tafamidis is a small molecule that has been demonstrated to stabilize transthyretin and is being developed for the treatment of TTR-CM. Tafamidis has already been approved in the European Union for the treatment of Transthyretin Familial Amyloid Polyneuropathy (TTR-FAP) in adult patients with stage 1 symptomatic polyneuropathy. It has also been approved in Japan by the Ministry of Health, Labor and Welfare (MHLW) to delay the peripheral neurological impairment of transthyretin familial amyloid polyneuropathy.

1.2. Background and Rationale

Amyloidosis is a severely debilitating condition induced by the accumulation of various insoluble fibrillar proteins, or amyloid, within the tissues in amounts sufficient to impair normal function. Different precursor proteins have been associated with amyloid cardiomyopathy, including immunoglobulin light chains (associated with primary or AL amyloidosis), serum amyloid A (associated with secondary or AA amyloidosis) and transthyretin (TTR) representing the most common inherited amyloidosis. Transthyretin (also referred to as pre-albumin), a 127-amino acid, 55 kDa protein that is primarily synthesized in the liver, is a transport protein of thyroxine and retinol-binding protein-retinol (vitamin A) complex (Blake 1978, Monaco 1995).[3,34] A mutation in TTR accelerates the process of fibrillogenesis whereby the tetrameric structure of the TTR protein dissociates leading to amyloid deposition (Nilsson 1975, Saraiva 2001).[36,45] Dissociation of the TTR tetramer into monomers is the initial and rate-limiting step in amyloidogenesis (Nilsson 1975, Saraiva 2001).[36,45]

Transthyretin amyloidosis can present as either a hereditary or an age-related disease. The major phenotypic presentations of TTR amyloidosis include transthyretin familial amyloid polyneuropathy (TTR-FAP), which can present with sensorimotor and autonomic polyneuropathy and transthyretin cardiomyopathy (TTR-CM), which can present in either a genetic variant or a wild-type form (the latter is also known as senile systemic amyloidosis or SSA).

More than 100 TTR single site variants have been identified and associated with TTR amyloidosis, and at least 22 mutations as well as wild-type protein are associated with transthyretin cardiomyopathy. The V122I (valine replaced by isoleucine at position 122) mutation is the most common, with an estimated prevalence of 3.3% in the African American population (Buxbaum 2006)[6] with variable clinical penetrance of approximately 30% (Jacobson 2011).[30]

In the elderly, wild-type (normal) TTR may become structurally unstable and result in deposition of amyloid fibrils, primarily in heart tissue, and may lead to diastolic dysfunction, restrictive cardiomyopathy and heart failure (Pages 1973, Saraiva 2001, Hammarström 2002, Quintas 2001).[45,25,38] The frequency of TTR amyloid deposition in cardiac ventricles reported from autopsy studies in subjects >80 years of age range from 1.8% (Jacobson 1997)[29] to 16.5% (Cornwell 1983)[10], with a rate of clinical cardiac disease premortem of 34% (Cornwell 1983).[10]

TTR-CM is a late onset disease with symptoms typically occurring in subjects aged 60 years or older, though the L111M variant may express TTR-CM in subjects at an earlier age.

Symptoms of TTR-CM are not mutation-type dependent and are typical of restrictive cardiac disease, and include dyspnea on exertion, orthostatic hypotension, and syncope, as well as conduction abnormalities, including bundle branch block, atrioventricular block, sinoatrial block, and atrial fibrillation. Objective measures of cardiac involvement include abnormal electrocardiogram (ECG) with findings including low voltage, left and right ventricular wall thickening by echocardiogram, and elevated cardiac biomarkers (Connors 2009).[8] These findings are non-specific for heart failure, making the diagnosis of cardiac amyloidosis difficult and resulting in likely under diagnosis of this condition (Falk 2011).[15]

Median survival from diagnosis for patients with TTR-CM was 41 months in a study of the V122I mutation and median survival was reported as 46 months for wild-type (Connors 2011).[9] Death in most patients with cardiac amyloidosis is from cardiac causes, including sudden death, heart failure, and myocardial infarction (Kyle 1996, Smith 1984).[31,47]

Except for symptom management, such as use of diuretics for symptoms of heart failure and pacemaker placement for cardiac arrhythmias, the only treatment option currently available for TTR-CM patients is orthotopic liver transplant. This may be combined with heart transplant, depending on organ availability, patient capacity to tolerate the combined transplant, and the severity of cardiac amyloidosis at the time of transplant. Transplantation of the liver removes the primary production site of amyloidogenic mutant TTR protein and replaces it with the production of wild-type TTR (Lewis 1994, Holmgren 1993).[33,27] The Familial Amyloidotic Polyneuropathy World Transplant Registry (FAPWTR) includes data on combined heart and liver transplant that indicates that this procedure is relatively infrequent, documenting 6 cases out of 575 transplantations (Herlenius 2004).[26] The mean age of those undergoing combined heart and liver transplant was older (58±5 years) than those undergoing liver transplant alone (40±11 years, $p<0.001$).

Tafamidis is an oral small molecule, under development by Pfizer, as a disease modifying therapy for TTR amyloid diseases. It binds to the thyroxine binding sites on the TTR tetramer, thereby preventing destabilization into the monomeric form. It has been demonstrated to bind selectively to TTR in human blood and slow fibril formation in vitro (Razavi 2003).[40] It binds to the 2 thyroxine binding sites with negative cooperativity, exhibiting dissociation constants of 2 nM [K_{d1}] and 154 nM [K_{d2}] (DeVit 2006)[11] and kinetically stabilizing the TTR tetramer when bound (Sekijima 2009).[46]

TTR stabilization has been hypothesized to lead to slowing or halting of disease progression. This hypothesis was confirmed in study Fx-005, a double-blind, placebo-controlled, 18-month study in subjects with TTR-FAP, in which those subjects receiving tafamidis had better neurologic outcomes compared with those receiving placebo. In order to improve the understanding of the natural history of TTR-CM, a longitudinal, observational clinical study of 29 subjects with either the V122I genetic variant (11 subjects) or wild-type (18 subjects) associated TTR-CM (Transthyretin Amyloid Cardiac Study; TRACS) was undertaken. A follow-up Phase 2 open-label interventional study (Study Fx1B-201) demonstrated TTR

stabilization in subjects with V122I and wild-type TTR-CM, an acceptable safety profile, and apparent stabilization of disease following 12 months of tafamidis 20 mg given once daily compared with the unmatched historical control cohort (TRACS). In study Fx1B-201, tafamidis effectively stabilized TTR in 34 of 35 (97.1%) subjects, representing both wild-type and V122I, at Week 6, with approximately 88% stabilized throughout the 12 months of the study. Of note, tafamidis has also been studied in TTR-FAP and effectively stabilized TTR in 98% of subjects as well as demonstrating effects relative to placebo on clinical measures (Coelho 2012).[7]

Study Fx-002 was a Phase 1 study designed to evaluate the safety, tolerability, and pharmacokinetics of orally administered tafamidis in healthy male and female volunteers at single doses up to 120 mg and 3 multiple escalating doses (15, 30 and 60 mg) administered as solution in comparison to placebo once daily over 14 days. Study Fx1A-109 was a Phase 1 study in healthy volunteers designed to evaluate the cytochrome P450 induction potential of tafamidis 20 mg administered for 14 days. In Fx-002, the mean (standard deviation) Cmax value on Day 14 for the 60 mg solution was 4.40 (1.16) µg/mL. The mean (standard deviation) Cmax on Day 14 for the 20 mg capsule was 2.66 (0.55) µg/mL in Fx1A-109.

There were no dose-limiting safety or tolerability issues noted during the Phase 1 program in healthy subjects up to a single dose of 480 mg or multiple doses up to 60 mg. Further, a single oral dose of 20 mg tafamidis was well tolerated by subjects with moderate or mild hepatic impairment. No cases of acute overdose with tafamidis have been reported.

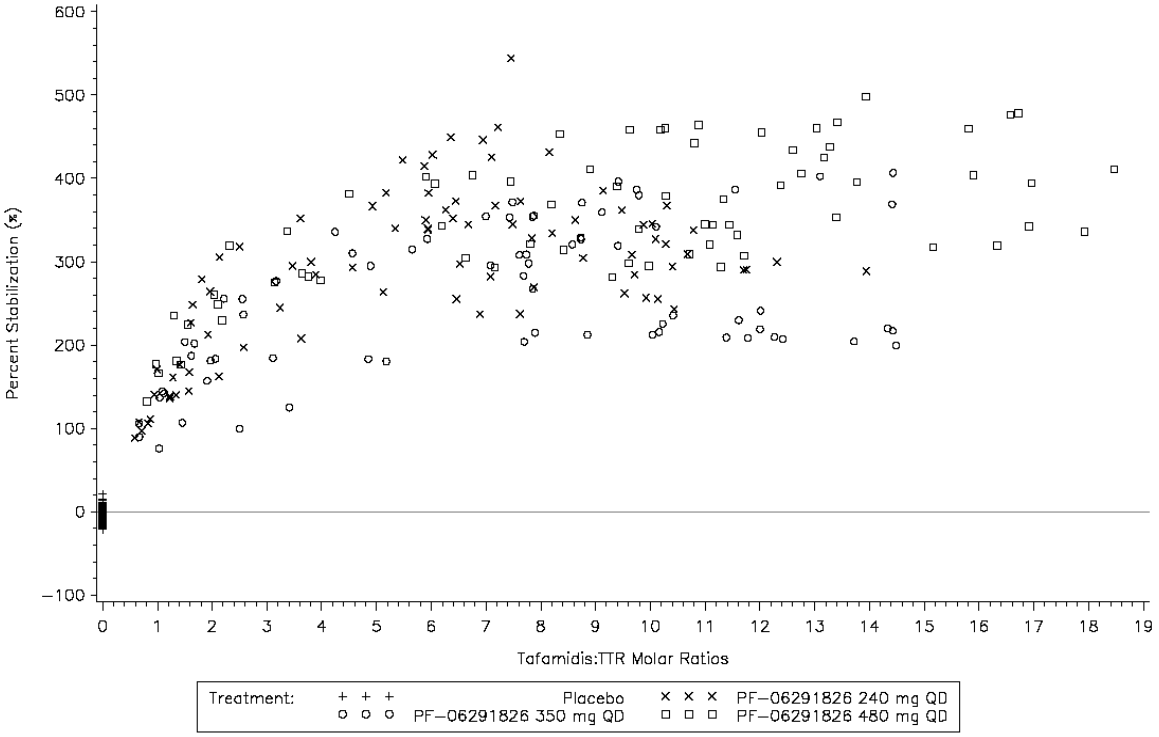
Study B3461040 was a Phase 1, randomized, double-blind, crossover, ascending dose escalation study to assess the safety and pharmacokinetics of tafamidis doses greater than 120 mg as oral solution in healthy subjects. Single doses of tafamidis up to 480 mg were well tolerated in the study population of healthy adult Asian men.

The transthyretin (TTR) % stabilization data from Study B3461040 (Figure 1) suggest that a plateau is achieved as the molar ratio of tafamidis: TTR plasma concentration (MR) increases. Based upon the data available prior to conducting Study B3461040, it was believed that exposures achieved following a tafamidis dose of 20 mg once daily (QD) were sufficient to approach the TTR % stabilization plateau. The data from Study B3461040 suggest that doses higher than 20 mg provide a greater degree of stabilization, as measured by the urea-based TTR stabilization assay. While the long-term risk-benefit of doses higher than 20 mg QD is unknown, it is reasonable to postulate that greater TTR stabilization has the potential to provide additional efficacy.

In order to calculate molar ratios at various tafamidis exposures, a TTR concentration must be assumed. Mean TTR concentrations observed at Baseline in Study Fx-005 (24.7 mg/dL) and in patients with V122I mutations in Study Fx1B-201 (13.5 mg/dL) and the Transthyretin Amyloid Cardiac Study (TRACS) (14.9 mg/dL) are assumed for the calculations that follow: a 20 mg QD tafamidis dose at steady state produces a mean MR in the range of 1.2 to 3.2 from mean minimum concentration at steady state ($C_{min,ss}$) to maximum concentration at steady state ($C_{max,ss}$), which is below the plateau region of the data depicted in (Figure 1).

Mean $C_{min,ss}$ to $C_{max,ss}$ following tafamidis doses of 80 mg are expected to produce MR values of 3.5 to 9.6, which are approaching or on the plateau region of TTR % stabilization.

Figure 1. Scatter Plot of TTR Percent Stabilization vs Tafamidis:TTR Molar Ratio by Treatment in Study B3461040



Abbreviations: TTR= transthyretin; QD = once daily
Source: B3461040 CSR Figure 14.4.7.2.1

Based upon the TTR % stabilization data, tafamidis doses of 20 and 80 mg will be used in Study B3461028. The 20 mg dose will provide additional safety and efficacy data for that previously studied dose in TTR-FAP. The 80 mg dose is approaching maximal TTR % stabilization, which has the potential for increased efficacy over the 20 mg dose.

The B3461031 study was a Phase 1 study designed to evaluate the effect of tafamidis on the corrected QT (QTc) interval in healthy volunteers. The primary objective was to characterize the effect of a supra-therapeutic tafamidis concentration (~20 µg/mL) on QTc interval relative to placebo in healthy volunteers. The primary analysis was to compare the time-matched mean differences in QTc interval using Fridericia's correction method (QTcF) between tafamidis and placebo at each post-dose time. The secondary ECG endpoint was to compare the mean difference in QTcF interval between moxifloxacin and placebo at the historical moxifloxacin median Tmax of 3 hours. A supra-therapeutic, single, 400 mg oral-dose of tafamidis solution in healthy volunteers demonstrated a lack of an effect on QTc

interval prolongation. Single doses of moxifloxacin 400 mg established that the study had adequate sensitivity to detect increases in QTc interval.

TTR-CM is a rare disease with very little available published information. Based on this, the natural history and disease progression of TTR-CM were prospectively evaluated in a non-interventional study involving 29 subjects (Transthyretin Amyloidosis Cardiac Study [TRACS]; Study Fx-001; Ruberg 2012).[41] In addition, subsequent to the TRACS study, an open-label, Phase 2 Study Fx1B-201 was initiated. This study involved 35 subjects with TTR-CM who received open-label tafamidis 20 mg QD for 12 months along with routine standard of care. The proportion of patients with the variant genotype was substantially lower in Fx1B-201 compared with TRACS.

1.2.1. Studies TRACS and Fx1B-201

In the Fx1B-201 study, 31 subjects had the wild-type genotype and 4 had the V122I genotype. The subjects were elderly (mean age approximately 76 years), with significant disease duration (approximately 8 years), and signs and symptoms of mild to moderate cardiac dysfunction (94% with NYHA Class I or II) at the time of enrollment. Age, sex, and age at TTR symptom onset were similar between the TRACS and Fx1B-201 studies. A larger percentage of subjects in the TRACS study had an NYHA class of III or higher (7/29, 24.1%) than in Study Fx1B-201 (2/35, 5.7%) at Baseline.

Following 12 months treatment with tafamidis, along with routine standard of care, 2/35 (5.7%) subjects died, 9/35 (25.7%) experienced at least one cardiovascular-related hospitalization, and 9/35 (25.7%) experienced the composite endpoint of death or cardiovascular-related hospitalization. Results were similar between the TTR genotype groups. A Kaplan-Meier analysis of survival from time of diagnosis for the study demonstrated an approximately 87.5% survival rate at 30 months. These data were numerically better than that reported in the TRACS historical control cohort (which it should be noted was not a matched cohort and had greater disease severity at Baseline), during which the 12-month rate of death, cardiovascular-related hospitalizations and death/cardiovascular-related hospitalizations were 6/29 (20.7%), 10/29 (34.5%) and 13/29 (44.8%), respectively.

Cardiac biomarkers (NT-proBNP, troponin I and T) at Baseline were elevated in study Fx1B-201. There were elevations in NT-proBNP over 12 months that were more apparent in the V122I than the wild-type population in the study. Troponin I and T, more specific markers of cardiac necrosis, remained relatively stable in the wild-type population, suggesting no substantial deterioration of cardiac status over 12 months of tafamidis treatment. These data are supported by the functional assessments of NYHA classification and 6-Minute Walk Test (Appendix 4). At 12 months, 75% of the subjects in Fx1B-201 had improved or preserved NYHA classification, with the overall population demonstrating minimal change on the 6-Minute Walk Test in distance walked (mean change from Baseline of -11 meters). This maintained functional walking capacity is in contrast to the deterioration observed in TRACS at 12 months (mean change from Baseline of -44 meters).

Non-invasive cardiac assessments demonstrated significant cardiac involvement at Baseline in study Fx1B-201, with substantial ventricular wall thickening on echocardiography and cardiac magnetic resonance imaging (MRI) and elevated intra-cardiac filling pressures on echocardiography. There were no consistent clinically relevant changes in the echocardiography parameters over time. For the wild-type subjects, who were the majority of subjects in the study, the deterioration in ejection fraction (-4.4%) and stroke volume (-1.9 mL) observed in the Fx1B-201 study was less than that observed in TRACS (-11.3% and -9.0 mL, respectively) at 12 months. Similar findings were observed in a subset of subjects that underwent cardiac MRI. In these subjects in the Fx1B-201 study, there was a decrease in the percent of left ventricle (LV) mass with amyloid observed at 12 months, while there was an increase in LV mass with amyloid observed in TRACS.

Baseline electrocardiogram and 24-hour Holter monitoring demonstrated substantial conduction and rhythm abnormalities, including bundle branch blocks and atrial fibrillation/flutter. There were no clinically relevant changes over time in these assessments, with perhaps slight improvement in cardiac autonomic function in study Fx1B-201 as demonstrated by improved heart rate variability indices.

Over the 12 months of tafamidis treatment in study Fx1B-201, quality of life and functional status was maintained, as assessed by the Short Form-36, patient reported health survey (SF-36), the Kansas City Cardiomyopathy Questionnaire (KCCQ),(Appendix 1.1) and the Patient Global Assessment (PGA) (Appendix 3). The majority of these results were also better when compared with TRACS.

Seven subjects participated in both TRACS (median follow-up 12.5 months, with range of 6-26 months) and Protocol Fx1B-201. All seven subjects completed 12 months of treatment with tafamidis. However, given the small number of subjects, it is difficult to assess whether disease progression was different during treatment with tafamidis as compared to standard of care in TRACS. The rate of cardiovascular-related hospitalization was similar between the two 12-month periods, with some evidence of stabilized cardiac function (ejection fraction and fractional shortening) observed following treatment with tafamidis.

The type and incidence of adverse events observed in study Fx1B-201 was not unexpected for this elderly subset of subjects with pre-existing cardiac disease related to TTR-CM. Two deaths were reported during the study. One subject died of a hemorrhagic stroke approximately 4 months after study start, while on anticoagulation medication and after sustaining a head injury resulting from a fall. The other subject was diagnosed with primary (light chain) amyloid cardiomyopathy, a disease for which tafamidis is not designed to be effective, approximately 11 months after starting the study. He died following complications of pleurodesis, for management of recurrent pleural effusions. The former event was unexpected and considered possibly related to study drug and the latter case was considered to be unrelated to study drug. In addition, one subject discontinued participation in Fx1B-201 to undergo temporal lobectomy for treatment of a glioblastoma multiforme, reported approximately 12 months after starting the study, which was considered unrelated to tafamidis and the subject died secondary to an intracranial hemorrhage. A second subject with a history of systolic and diastolic heart failure, worsening heart failure, and increasing

falls, which were assessed as possibly related to tafamidis, died approximately 2 months after study completion of an unknown cause. The death was assessed as unrelated to tafamidis.

The most frequent adverse events overall were related to symptoms and episodes of heart failure (dyspnea, cardiac failure and edema). Eighteen (51.4%) subjects reported at least one Treatment Emergent Adverse Events (TEAE) that was considered at least possibly related to study medication. The most common (>5%) treatment-related TEAEs included urinary tract infection (20.5%), balance disorder (14.3%), ageusia (8.6%), constipation, diarrhea, edema peripheral, fall, weight increased, decreased appetite and dyspnea (5.7% each). The majority (≥85%) of subjects experienced TEAEs considered mild or moderate in severity. One adverse event (AE) of hyperkalemia, reported during a hospitalization for decompensated heart failure and associated with acute renal failure, was considered life-threatening and not related to tafamidis.

In study Fx1B-201, a total of 15 (42.9%) subjects reported 41 treatment-emergent serious adverse events (SAEs), with the majority cardiac in nature. Serious adverse events reported by more than 1 subject included cardiac failure congestive (reported in 9 patients), atrial fibrillation and fall (3 subjects each), cardiac failure, syncope (2 subjects each). The reasons for hospitalizations were similar to those reported during TRACS, again primarily cardiac in nature (eg, worsening congestive heart failure).

Renal function was abnormal overall at Baseline, and suggestive of pre-renal azotemia with blood urea nitrogen (BUN) elevated to a greater degree than creatinine. BUN remained stable in subjects with wild-type disease but there was evidence of progressive worsening in the four African-American subjects with V122I. NT-proBNP and troponin I and T were elevated at Baseline, but remained stable through 12 months in subjects with wild-type TTR. Although increases over the 12-month study were noted in subjects with V122I in these cardiac markers, it is not known if the elevations were related to worsening cardiac or renal function. There were no other clinically relevant changes in mean laboratory parameters over time.

There were no clinically relevant changes in vital signs, or in the proportion of subjects with orthostatic hypotension on treatment. There were no apparent adverse effects of tafamidis on cardiac rhythm or conduction, including cardiac repolarization.

The adverse events reported for subjects during study Fx1B-201 largely reflect underlying disease, co-morbid conditions, and elderly status. Given the caveat that this study did not have a control group, there were no apparent safety trends related to drug therapy, suggesting that an oral daily dose of 20 mg tafamidis over 12 months was well tolerated in TTR-CM subjects.

TRACS and Fx1B-201 have provided not only Baseline data on a variety of cardiac functions in this subject population, but change in these functions over time. This current interventional study is designed to evaluate whether stabilization of TTR by tafamidis can modify clinical outcomes as well as specific cardiac parameters associated with TTR-CM. The study medication was referred to in previous study protocols as Fx-1006A. To simplify

discussions in the text of this protocol, the term 'tafamidis' is used to refer to the study medication and dosing regimen.

1.2.2. Dose Rationale

This protocol will employ tafamidis meglumine at 20 mg and 80 mg doses compared with placebo. The 20 mg dose of tafamidis has been used previously in both polyneuropathy and cardiomyopathy trials. A range of tafamidis exposures has been assessed in clinical pharmacology studies in healthy volunteers that include the concentrations expected with an 80 mg dose. The addition of the 80 mg dose, which is expected to result in near maximal TTR stabilization, will permit exploration of a higher dose to assure that efficacy and safety have been explored across a range of adequately separated doses.

1.2.3. Study Rationale

This study is being conducted to evaluate the efficacy and safety of tafamidis in comparison to placebo for the treatment of TTR-CM. Tafamidis is a novel specific stabilizer of both wild-type and amyloidogenic variants of TTR. Tafamidis binds to TTR at the thyroxine binding sites and inhibits TTR tetramer dissociation, the rate-limiting step in the amyloidogenic process. By stabilizing the tetrameric native state of TTR, tafamidis increases the activation barrier associated with tetramer dissociation and therefore mimics the tetrameric stabilization effect observed with naturally occurring protective trans-suppressor variants. It is hypothesized that tafamidis would stop or slow the progression of TTR-CM and therefore represent a disease modifying therapy.

Complete information for this compound may be found in the Single Reference Safety Document (SRSD), which for this study is the Investigator Brochure (IB).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of this study is to assess the efficacy of an oral dose of 20 mg or 80 mg tafamidis meglumine soft-gel capsules based on all-cause mortality and on frequency of cardiovascular-related hospitalizations as well as to assess safety and tolerability in comparison to placebo. Tafamidis or placebo will be administered once daily, in addition to standard of care, for 30 months in subjects diagnosed with variant or wild-type TTR cardiomyopathy (TTR-CM).

2.2. Endpoints

This protocol will use an independent Endpoint Adjudication Committee (EAC) to determine whether certain investigator-reported events meet the definition of disease-related efficacy endpoints, using pre-defined endpoint criteria thereby maintaining scientific integrity of the study. Sites will submit a Serious Adverse Event notification for all deaths and hospitalizations, as outlined in Section 8.14.1

The Endpoint Adjudication Committee is the primary group responsible for adjudicating all potential endpoint events reported in this study. This Committee will conduct a review of events reported by trial investigators blinded for treatment assignment to determine whether they meet protocol-specified criteria for endpoint reporting. The EAC is independent of Pfizer. Inclusion of an independent EAC is justified in order to comply with regulatory and industry standards**.** In the event there is insufficient information for the adjudication process to classify either a mortality or hospitalization as cardiovascular related or not cardiovascular related, then the event will be classified as "indeterminate". In the adjudication process, cases with at least some information indicating a contributory cardiovascular cause, including ambiguous cases, will be adjudicated to the cardiovascular-related category. Details of the actions and responsibilities of the EAC can be found in the EAC Charter and EAC Guidelines, the latter of which have been incorporated into the EAC Charter.

2.2.1. Primary Analysis

The primary analysis uses a hierarchical combination, applying the method of Finkelstein-Schoenfeld (Finkelstein 1999)[16] to:

1. All-cause mortality and

2. Frequency of cardiovascular-related hospitalizations over the duration of the trial, which is defined as the number of times a subject is hospitalized (ie, admitted to a hospital) for cardiovascular-related morbidity.

2.2.2. Key Secondary Endpoints:

1. Change from Baseline to Month 30 in the distance walked during 6-Minute Walk Test (6MWT).(Appendix 4)

2. Change from Baseline to Month 30 in the Kansas City Cardiomyopathy Questionnaire Overall Score (KCCQ-OS).(Appendix 1.1)

2.2.3. Secondary Endpoints:

1. Cardiovascular-related mortality.

2. Frequency of cardiovascular-related hospitalization.

3. All-cause mortality.

4. TTR stabilization at Month 1.

2.2.4. Exploratory Endpoints:

1. Frequency of all-cause hospitalization.

2. Cardiovascular-related days hospitalized.

3. All-cause days hospitalized.

4. All-cause mortality and the frequency of all-cause hospitalization using the Finkelstein-Schoenfeld analysis.

5. All-cause mortality and cardiovascular-related days hospitalized using the Finkelstein-Schoenfeld analysis.

6. Cardiovascular-related mortality and frequency of cardiovascular-related hospitalization using the Finkelstein-Schoenfeld analysis.

7. TTR stabilization at each time point other than Month 1.

8. TTR concentration at each time point.

9. Change from Baseline at time points other than Month 30 in the 6-Minute Walk Test (6MWT).(Appendix 4).

10. Change from Baseline at time points other than Month 30 in the Kansas City Cardiomyopathy Questionnaire Overall Score (KCCQ-OS).(Appendix 1.1).

11. Change from Baseline at each time point in the Kansas City Cardiomyopathy Questionnaire domain scores (Physical limitation, Symptom stability, Symptom frequency, Symptom burden, Self-efficacy, Social limitation, and Quality of life) and domain summary scores (Functional summary and Clinical summary).

12. Change from Baseline at each time point in EuroQoL-5 Dimensions (EQ-5D-3L) (Appendix 2) Index Score and visual analog scale (VAS) scores.

13. Patient Global Assessment at each time point (Appendix 3).

14. New York Heart Association classification (NYHA) at each time point.

15. Change from Baseline at each time point in modified Body Mass Index.

16. Change from Baseline at each time point in NT-proBNP concentration.

17. TTR oligomer concentration at each time point.

18. Change from Baseline at each time point in select echocardiographic parameters (See Section 7.6.5 for complete list), including:

    a. End-diastolic interventricular septal wall thickness (mm);

    b. Left ventricle posterior wall thickness (mm);

    c. Left ventricular ejection fraction (%);

    d. Left ventricular stroke volume (mL);

e. Global longitudinal strain;

f. Circumferential strain mid global;

g. Radial strain mid global.

Safety and tolerability will be assessed with adverse event reporting as well as the conduct of ECGs, clinical laboratory testing, vital signs, and physical examinations.

3. STUDY DESIGN

This is a Phase 3, multicenter, international, three-arm, parallel design, placebo-controlled, randomized study with a 30-month double-blind treatment phase, to determine efficacy, safety and tolerability of tafamidis on clinical outcomes in subjects with either transthyretin genetic variants or wild-type transthyretin resulting in amyloid cardiomyopathy (TTR-CM).

There will be approximately 400 subjects enrolled in the study in a 2:1:2 ratio (placebo:20 mg:80 mg). The subjects will be allocated to the 3 arms of the study in the following manner: n=160 in the placebo arm, n=80 in the 20 mg arm, and n=160 in the 80 mg arm. Subjects who experience adverse events that may be associated with poor tolerability to treatment with tafamidis that may impact dosing adherence have the option of blinded treatment re-assignment and potential dose reduction (see Section 5.5). Subjects will be stratified during enrollment by TTR genotype (variant and wild-type) and structured such that greater than 30% of randomized subjects have a TTR mutation and greater than 30% of subjects have a diagnosis of wild-type TTR cardiomyopathy, with the intent to enroll comparable numbers between the variant and wild-type groups.

Enrollment may be closed for either wild-type or variant stratum in order to enroll at least 30% of subjects with each TTR genotype (wild-type and variant).

Additionally, stratification to treatment assignment will be done for Baseline severity of disease based on NYHA classification (NYHA Class I and NYHA Classes II and III combined). Stratification will be implemented in order to maintain a balance of both TTR genotype and disease severity across the treatment assignments. The site will ensure a Month 30 follow-up contact to determine the subject's vital status and whether the subject has had a heart and / or liver transplant or implantation of cardiac mechanical assist device. Upon completion of the study at the Month 30 visit, subjects may be eligible for -treatment with tafamidis in a separate extension study (B3461045), which will permit the collection of additional safety and efficacy data, and may include the assessment of hospitalizations, mortality, and other outcomes relating to disease progression. For the purpose of this study, 30 months is defined as 910 days. Eligibility for the extension study (B3461045) requires subject participation in this study at least through Day 896 (Month 30 minus 2 weeks).

4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

4.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team, before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Evidence of a personally signed and dated Informed Consent Document indicating that the subject (or a legal representative) has been informed of all pertinent aspects of the study and evidence of a personally signed and dated Release of Medical Information Form regarding access to medical records as well as vital status / transplant status follow-up by the site with the subject or the subject's caregivers 30 months after study randomization. In some cases, sites may combine these two forms into one form, as is their standard practice.

2. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures,

3. Age greater than or equal to 18 and less than or equal to 90 years old at the time of randomization,

4. Medical history of Heart Failure (HF) with at least 1 prior hospitalization for HF or clinical evidence of HF (without hospitalization) manifested by signs or symptoms of volume overload or elevated intracardiac pressures (eg, elevated jugular venous pressure, shortness of breath or signs of pulmonary congestion on x-ray or auscultation, peripheral edema) that required/requires treatment with a diuretic for improvement,

5. Subject has documented TTR amyloid cardiomyopathy in accordance with institutional site standard of care, which is defined as:

    a. Variant TTR amyloid cardiomyopathy defined by all of the following:

        - presence of a variant TTR genotype associated with cardiomyopathy and presenting with a cardiomyopathy phenotype (eg, a history of congestive heart failure),

            1. TTR genotyping is required at Screening unless documentation (ie, original laboratory result, or copy) of a prior determination of a TTR genotype is produced,

2. Subjects with a confirmed diagnosis of mutant (variant genotype) TTR-CM with concurrent monoclonal gammopathy of undetermined significance (MGUS) based on serum or urine light chain determinations, should be tested in the same manner as in the case of equivocal immunohistochemistry for subjects with wild type TTR-CM below,

- Evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness > 12 mm,

- Presence of amyloid deposits in biopsy tissue, such as fat aspirate, salivary gland, median nerve connective tissue sheath, or cardiac (amyloid demonstrated per appropriate stain such as Congo red or alcian blue stain).

b. Wild-type TTR amyloid cardiomyopathy defined by all of the following:

- absence of a variant TTR genotype,

- evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness > 12 mm,

- presence of amyloid deposits in biopsy tissue, such as fat aspirate, salivary gland, median nerve connective tissue sheath, or cardiac (amyloid demonstrated per appropriate stain such as Congo red or alcin blue stain),

- TTR precursor protein identification by immunohistochemistry, scintigraphy or mass spectrometry (Ruberg and Berk 2012, Dungu et al, 2012).[41,13]

1. In the case where immunohistochemistry (IHC) outcome is equivocal such as staining suggestive of lambda or kappa light chains, additional confirmatory testing is required to confirm the diagnosis of TTR cardiomyopathy. This confirmatory test may be performed using one of the following: (a) mass spectrometry (b) immunohistochemistry with electron microscopy or immunoelectron microscopy or immune-gold microscopy (c) scintigraphy with tracer eg 99mTC-DPD [99mTC-3,3-diphosphono-1,2-propano-dicarboxylic acid], 99mTC- PYP [Pyrophosphate] and also 99mTC-HMDP [hydroxymethylene diphosphonate](Ando Y 2013, Glaudemans 2014, Bokhari S 2014, Bokhari S 2013).[2,18,5,4]

6. Biopsy, used to determine the presence of amyloid and demonstration of TTR precursor protein, must be done during Screening or documented as having been performed previously,

7. Subject must be able to read in native language and complete self-administered questionnaires independently,

8. Subject's symptoms of HF are optimally managed and clinically stable with no cardiovascular-related hospitalizations within 2 weeks prior to Baseline, as assessed by the Principal Investigator,

9. Male and female subjects of childbearing potential and at risk for pregnancy must agree to use two highly effective methods of contraception throughout the study and for at least 28 days after the last dose of assigned treatment. A subject is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active,

10. Subject must have a Screening visit NT-proBNP concentration > 600 pg/mL (the conversion factor from conventional pg/mL to SI units is to divide by 8.45),

11. Subjects must be able to complete > 100 m on the 6-Minute Walk Test at Screening,

4.2. Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

1. Subjects with echocardiogram assessment at Screening that is not deemed interpretable by the central echocardiogram reader for the measurement of wall thickness.

2. Subjects using non-steroidal anti-inflammatory drugs (NSAIDs) that are not allowable in the protocol within 30 days prior to the Baseline visit (see Section 5.8.1).

3. Subjects with an mBMI below 600.

4. Subjects with a history of drug or alcohol abuse within the past 5 years that in the opinion of the investigator would interfere with compliance with study procedures or follow-up visits.

5. Subjects taking or have previously taken tafamidis.

6. Subjects requiring treatment with calcium channel blockers (eg verapamil, diltiazem) or digitalis.

7. Subjects with primary (light chain) amyloidosis.

8. Subjects who have prior liver or heart transplantation, or implanted cardiac mechanical assist device.

9. Subject has known or suspected hepatitis B, C, Human Immunodeficiency Virus (HIV) infection or positive serology for hepatitis B (HBsAg), hepatitis C (anti-HCV), or HIV.

10. Subjects with renal failure requiring dialysis and/or have an estimated glomerular filtration rate (eGFR) of < 25 mL/min./1.73 m^2.

11. Subjects with urinary retention requiring self-catheterization.

12. Subjects who are investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the Investigator, or subjects who are Pfizer employees directly involved in the conduct of the trial.

13. Subjects who have symptoms indicative of New York Heart Association Classification IV at the Screening or Baseline visit.

14. Subjects with liver function test abnormalities (alanine transaminase and/or aspartate transaminase) greater than 2 times the upper limit of normal that are considered to be due to reduced liver function or active liver disease.

15. Subjects with participation in studies involving investigational drug(s) (Phases 1-4) within 30 days before the current study begins and/or during study participation. For diflunisal, tauroursodeoxycholate and doxycycline, this time period will also be within 30 days before the Baseline visit and/or any time during study participation.

16. Subjects with other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

17. Subjects who are pregnant females; breastfeeding females; male subjects with partners currently pregnant, males and females of childbearing potential who are unwilling or unable to use two (2) highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days, after last dose of investigational product.

18. Subjects with a history of sustained ventricular tachycardia or aborted ventricular fibrillation or with a history of atrioventricular (AV) nodal or sinoatrial (SA) nodal dysfunction for which a pacemaker is indicated but will not be placed.

19. Subjects with heart failure that in the opinion of the investigator is on the basis of ischemic heart disease (eg prior myocardial infarction with documented history of cardiac enzymes and ECG changes), or uncorrected valvular disease and not primarily due to transthyretin amyloid cardiomyopathy.

4.3. Life Style Guidelines

4.3.1. Contraception

In this study, fertile male subjects and female subjects who are of childbearing potential will receive tafamidis, which has been associated with teratogenic risk. Subjects who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use 2 methods of highly effective contraception throughout the study and for

28 days after the last dose of investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected 2 appropriate methods of contraception for the individual subject and his/her partner(s) from the list of permitted contraception methods (see below) and will confirm that the subject has been instructed in their consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the subject of the need to use 2 highly effective methods of contraception consistently and correctly and document the conversation, and the subject's affirmation, in the subject's chart. In addition, the investigator or designee will instruct the subject to call immediately if 1 or both of the selected contraception methods is discontinued or if pregnancy is known or suspected in the subject or partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal), provided the subject or male subject's partner plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness,

2. Correctly placed copper-containing intrauterine device (IUD),

3. Male condom or female condom used WITH a separate spermicide product (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate,

4. Male sterilization with absence of sperm in the post-vasectomy ejaculate,

5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

4.4. Sponsor Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the trial is documented in the study contact list located in the coordinator's manual.

To facilitate access to appropriately qualified medical personnel on study related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, subject study number, contact information for the investigational site and contact details for a help desk in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subjects participation in the study. The help desk number can also be used by investigational staff if they are seeking advice on medical questions or problems, however it should only be used in the event that the established communication pathways between the investigational site and

the study team are not available. It is therefore intended to augment, but not replace the established communication pathways between the investigational site and study team for advice on medical questions or problems that may arise during the study. The help desk number is not intended for use by the subject directly and if a subject calls that number they will be directed back to the investigational site.

5. STUDY TREATMENTS

5.1. Allocation to Treatment

Investigators will confirm the eligibility of each subject to meet inclusion/exclusion criteria. An Interactive Response Technology (IRT) system will assign a unique subject identification number sequentially to each subject who has signed the informed consent document (ICD). This identifying number will be retained throughout the duration of the study participation.

Subject eligibility for participation in the treatment phase of the protocol will be determined following the assessments during the Screening period and at the Baseline (Day 1) visit. Subjects will be screened for eligibility and those, in the judgment of the investigator, who meet the inclusion criteria and do not meet the exclusion criteria, will be randomized. There will be a treatment assignment stratification by TTR genotype (variant or wild-type) as well as by Baseline severity (NYHA Class I and NYHA Classes II and III combined). Subjects will be assigned to blinded treatment with either tafamidis 20 mg or 80 mg or matching placebo once daily, in addition to standard of care (eg, diuretics) for 30 months. Other than Week 2, Month 1 and Month 3, study visits will be at 3-month intervals (Month 6, 9, 12, etc.). Subjects must return for their appointment before their blinded study drug supply is exhausted. Subjects must bring all of their study medication wallets and their Subject Daily Dosing Diary to each appointment. The site will collect all study medication wallets dispensed at the previous visit and dispense a new set of study medication wallets and a Subject Daily Dosing Diary to the subject.

5.2. Breaking the Blind

The reason for breaking the blind for an individual subject may include the following:

1. A serious, unexpected/unlisted, treatment-related event for reasons of subject safety.

2. An urgent safety measure taken by the investigator or Pfizer to protect subjects against immediate hazard to health.

3. A potentially life threatening drug interaction.

4. Ethical considerations such as a medical emergency where understanding the treatment allocation is necessary to adequately manage the subject's condition. In this case, an attempt should be made to contact the study clinician or another member of the study team.

Whenever possible, the investigator or sub-investigator should consult with a member of the study team (eg, the clinical trial manager or the monitor) prior to breaking the blind for an individual subject. After reviewing and approving the investigator's request, the study clinician will provide written authorization (email) to the investigator to break the blind.

If unable to contact a member of the study team, the investigator may break the blind for a given subject experiencing an SAE or other medical emergency where knowledge of the treatment assignment will affect treatment decisions.

Breaking the blind will be done electronically and instructions will be given at a training session for the protocol.

5.3. Dosing Adherence

Subjects will be instructed to take the medication on a daily basis. They will also be instructed to bring all of their study medication back to the study site, including used and unused study medication wallets, at each scheduled study visit so that the total amount of drug taken can be determined and unused medication collected by site personnel. Study drug capsule count will be performed at each scheduled visit for all subjects or as per local regulations. The need for adherence with study drug administration will be reinforced at each study visit.

For the purpose of promoting dosing adherence, the sites will calculate the number of days dosed divided by the number of days participating in the study for each study visit to provide a measure of treatment adherence. As part of study data analysis, subjects will be considered to be adherent to the dosing requirements of the study if they have taken 4 capsules of study medication per day on at least 80% of the days of study participation. Subjects with less than 80% dosing adherence will be excluded from the per protocol analysis set.

Subjects will be randomized to blinded therapy with either 20 mg or 80 mg of tafamidis or placebo. Individual subjects with tolerability issues that could impact dosing adherence will have the option to receive blinded dose reduction of their dose. See Section 5.5 regarding the decision and procedures for blinded dose reduction due to poor tolerability.

5.4. Drug Supplies

In order to achieve the proper dosage and maintain the blind in the study, capsules will be dispensed in a blinded fashion to achieve a daily dose of 4 capsules. Each dose of 4 capsules will consist of either 3 capsules of blinded placebo and 1 capsule of blinded tafamidis 20 mg, 4 capsules of blinded tafamidis 20 mg, or 4 capsules of blinded placebo.

Dosage Level	Compound	Appearance	Number of Capsules Per Day (Dose)
Tafamidis meglumine 20 mg	PF-06291826	Oblong soft gelatin capsules	1 (Tafamidis 20 mg capsule) 3 (Placebo capsules)
Tafamidis meglumine 40 mg (in the event of blinded dose reduction for the 80 mg dose)	PF-06291826	Oblong soft gelatin capsules	2 (Tafamidis 20 mg capsules) 2 (Placebo capsules)
Tafamidis meglumine 80 mg	PF-06291826	Oblong soft gelatin capsules	4 (Tafamidis 20 mg capsules)
Placebo for Tafamidis		Oblong soft gelatin capsules	4 (Placebo capsules)

5.4.1. Dosage Form and Packaging

Tafamidis meglumine 20 mg (and matching placebo) in soft gel capsules will be packaged as 7 tri-fold study medication wallets in each carton with each wallet labeled 1 through 7. Each of the study medication wallets will be packaged with enough medication for 15 days of dosing. Subjects will be dispensed 1 carton containing 7 study medication wallets. This will provide enough study medication for each 3-month dosing period plus 1 extra study medication wallet to allow for flexibility in clinic visit scheduling (total of 105 days' supply). Written dosing instructions will be supplied to subjects. Subjects should be instructed to only dose from 1 study medication wallet each day. Subjects should take 4 capsules one time a day with water. Each 4-capsule daily dose is packaged on a separate row in the study medication wallet with "Date ____" printed beside each daily dose. Subjects should be instructed to dose each day from a single row, and write in the date that the dose was taken. Subjects should be instructed to complete dosing from one study medication wallet prior to starting dosing from the next consecutively numbered study medication wallet.

5.4.2. Preparation and Dispensing

Drug (or matching placebo) will be dispensed at Baseline (Day 1), Month 3, and at every 3-month visit thereafter using an IRT system.

5.5. Administration

Subjects will be instructed to take 4 capsules per day from an individual row on the dispensed study medication wallet and to take the capsules with a glass of water. Subjects will swallow the study medication whole, and will not manipulate or chew the medication prior to swallowing. Subjects will be instructed to dose at a consistent time of day. Subjects will be instructed to start taking their medication each day in the morning (AM dosing); however, it is permitted for subjects to take his/her medication in the PM prior to a clinic visit when the timing of pharmacokinetic (PK) sample collection is prohibitive for adherence with AM dosing. Subjects should not take an extra dose of medication in the event that a dose from a previous day is missed and should resume dosing 4 capsules per day from an individual row on the study medication wallet at the next planned dosing time. Similarly, if multiple doses are missed in succession, the subject should resume dosing at the next planned dosing time without taking additional doses to make up for those doses that were missed. Instructions on dosing are provided on the Subject Daily Dosing Diary.

At the end of each visit, sites will instruct subjects, in writing on the front of the Subject Daily Dosing Diary, when to take their medication prior to their next study visit. This is especially important if the next visit has a collection of blood sample(s) for PK analysis. Knowing the actual time of dosing is essential for appropriate analysis of samples for TTR stabilization, TTR and oligomer concentration, and for tafamidis pharmacokinetic measurements, as required and specified in Section 7.7.2 and Section 7.7.6. On the day of the study visit, subjects will write the actual time that they took their medication in the Subject Daily Dosing Diary and the site staff will record this dosing time in the case report form (CRF). On specified study days (Months 1, 18, and 24), subjects will take their medication during the clinic visit and subjects will be reminded to not take their daily dose on those days until instructed by clinic staff.

Subjects should be instructed not to take more than 4 capsules when taking their daily blinded therapy. It should also be noted that at Month 6 and Month 12 visits, dosing should take place 7 hours (± 2.5 hours) prior to the timing of PK sample. On the day prior to Month 6 and Month 12 visits, subjects are permitted to take their usual AM dose and then take the next day's dose in the PM if necessary to adhere to the PK sampling schedule.

In the event that subjects experience adverse events that may be associated with the tolerability of treatment with tafamidis that may impact dosing adherence, they should return to the clinic with their medication. If the investigator assesses that the tolerability issue is persistent and anticipated to impact dosing adherence and that the subject's safety is not compromised by continuing treatment, then the subject may receive blinded treatment re-assignment and potential dose reduction.

Prior to blinded dose reduction, the site should collect a PK sample, noting the actual time of last dosing and the actual time of PK sample collection. The site personnel will enter the subject's study-specific identification (SSID) number into the IRT system and request blinded dose reduction. The IRT system will provide a new container number for blinded treatment re-assignment for this subject. If the subject was receiving the 80 mg dose, then the re-assignment will be to 40 mg. If subject was receiving placebo or the 20 mg dose, they will be maintained on that dose but will still receive a new container number in order to maintain the blind. If poor tolerability continues following the blinded re-assignment, the site has the option to discontinue dosing for this subject and to terminate study participation. In the event of early study discontinuation, the site staff will follow-up on the subject's vital status / transplant status 30 months after randomization.

5.6. Drug Storage

The investigator or an approved representative, eg, pharmacist, will ensure that all investigational products, are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements. All investigational product should be stored at controlled room temperature 15-25° C (59-77° F). Investigational products should be stored in their original container and in accordance with the label.

Any storage conditions stated in the SRDS will be superseded by the storage conditions stated on the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure which ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

Site staff will instruct subjects on the proper storage requirements for take home investigational product.

5.7. Drug Accountability

At each scheduled clinic visits starting at Month 1; subjects will bring their Subject Daily Dosing Diary and their study medication wallets with them to the site. Beginning at the Month 3 visit, subjects will return used Subject Daily Dosing Diary and study medication wallets and site personnel will collect any unused medicine, determine dosages taken, and store returned drug for disposition. See Section 5.3 for documentation of dosing adherence.

The investigator's site must maintain adequate records documenting the receipt, use, loss, or other disposition of the drug supplies as outlined in the in the monitoring plan.

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site).

5.7.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). 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, and all destruction must be adequately documented.

5.8. Concomitant Treatments

Medications taken within 28 days before the first dose of trial medication will be documented as a prior medication. Medications taken after the first dose of trial medication will be documented as concomitant medications.

Concomitant Treatment is defined as ongoing or initiated at any time on or after Baseline (Day 1) of the study through the final study visit. Concomitant treatments include any substance ingested, injected, absorbed, inhaled, or otherwise enters the body for a therapeutic purpose regardless of number of doses taken. This includes prescription and over-the-counter medicines, vitamins, and herbal remedies.

Subjects may use supplements and medications during the course of the study with the exception of those listed in Section 4.2 and Section 5.8.1. Medication considered to be standard of care are permitted but should be recorded on the CRF.

Standard of Care: Medications indicated as standard of care should be stabilized for at least 4 weeks of therapy (other than diuretics) prior to Baseline.

Changes in diuretic dose are permitted within 4 weeks of the Baseline visit.

5.8.1. Contraindicated Therapies

Use of NSAIDs other than those noted below is prohibited. Some NSAIDs, like diflunisal, can bind to the thyroxine binding sites on transthyretin (Almeida 2004).[1] Subjects must discontinue use of diflunisal at least 30 days prior to the Baseline visit (Day 1). Permitted NSAIDs include: acetylsalicylic acid, etodolac, ibuprofen, indomethacin, ketoprofen, nabumetone, naproxen, nimesulide, piroxicam, and sulindac. Use of any other NSAIDS requires agreement with the Sponsor's clinician or medical monitor.

1. Use of any investigational therapy during the study is not permitted.

2. Use of diflunisal or any other investigational therapy during the study is prohibited. The presence of diflunisal in the blood will be measured at Screening and at various times throughout the study in order to document whether the subjects are taking a contraindicated medication so that they can be appropriately counselled. Such subjects will be handled as protocol violators in the analysis as described in the Statistical Analysis Plan.

3. Additionally, the use of tauroursodeoxycholate and doxycycline is not permitted.

4. Digitalis and calcium channel blockers (eg verapamil, diltiazem) are prohibited concomitant medications because they bind to amyloid fibrils and may lead to increased toxicity (Gertz 1985, Rubinow 1981, Rapezzi 2010).[17,44,39] If the agent is to be stopped, it must be at least 30 days before Baseline.

6. STUDY PROCEDURES

Every effort should be made to ensure that scheduled visits are completed according to the Schedule of Activities on the prescribed days and protocol required tests and procedures are completed as described. From time to time there may be circumstances, such as a constraint on travel for health-related reasons, that a clinic visit may not be possible. In these cases, with prior discussion and approval from the sponsor, alternative options for completing the visit may be considered. Additionally, visits should be completed as close to the scheduled timeframe as possible but not to exceed ±1 week of the target date for the Month 1 visit and ± 2 weeks of the target dates for subsequent visits.

The duration of this study is 30 months. Follow-up visit dates should be based on the date of the Baseline visit, not the date of the previous follow-up visit. If the Baseline visit, for example, is on the 15th of the month, the Month 1 visit is to be scheduled on the 15th of the next month ± 1 week). The Month 3 visit is to be scheduled on the 15th of the 3rd month from the Baseline visit ± 2 weeks).

The Month 30 visit is to be scheduled 910 days following the Baseline visit (± 2 weeks), and can be determined by the use of the Visit Calculator, located in Firecrest.

6.1. Screening Period

The following evaluations will be performed and laboratory samples collected for all subjects during the Screening Period prior to starting drug (eg, Day -45 to Day -10). If tests cannot be performed, if tests need to be repeated or if there are extenuating circumstances the Screening period may be extended following written authorization from the study clinician. The duration of the Screening extension will be no more than 2 weeks.

At the discretion of the investigator, isolated abnormal tests can be repeated for confirmation. However, the entire panel should not be repeated. In the event the repeated test confirms an abnormal value, no further testing is necessary. The abnormal test value from the confirmatory test will be entered into the database and the subject will be considered a Screen failure. If the repeat test does not confirm the abnormal value (ie, it is within the normal range), the investigator is required to again repeat the specific laboratory test. If this further repeat test confirms a value within the normal range, the last repeated normal value is entered into the database. If the further repeat test value is abnormal, this value will be entered into the database and the subject will be considered a Screen failure.

Written subject informed consent will be obtained prior to any study-related procedures.

The sites will assure that laboratory procedures are performed to allow sufficient time for returning results to the site for evaluation. The following procedures will be conducted during the Screening Period:

1. Medical History (including history of heart failure),
2. Smoking and alcohol classification,
3. Full physical examination including weight and height,
4. Single 12-lead ECG - perform ECGs prior to any blood collection or blood pressure measurements,
5. Echocardiogram (must have an end-diastolic interventricular septal wall thickness of >12 mm and assessment for study eligibility will be based on a central laboratory reading). See Section 7.6.5 for required measurements,
6. Vital signs (systolic and diastolic blood pressure supine and standing, pulse rate supine and standing, respiration rate, and body temperature),
7. Tissue biopsy (repeat not required if there is documentation by mass spectrometry, immunohistochemistry or scintigraphy of amyloid deposition from a prior biopsy). The original laboratory result, or copy will be part of the source documentation,
8. Collect blood, and urine samples for the following clinical laboratories:
    a. Hematology;
    a. Serum Chemistry;
    b. Coagulation (INR, PT);
    c. Serology for Hepatitis B (HBsAg), Hepatitis C (anti-HCV), and HIV;
    d. Serum and urine test for primary light chain amyloidosis (AL) Section 7.6.8;
    e. Urinalysis;
    f. Genotyping - not needed for subjects with prior documented genotyping. In such instances, the original laboratory result, or copy will be filed as source documentation;
    g. Urine pregnancy test – for women of childbearing potential.
9. Collect blood samples for NT-proBNP and troponin I.
10. Collect blood sample for diflunisal concentration (Section 7.7.3).

11. 6-Minute Walk Test (Appendix 4).

12. NYHA classification.

13. Documentation of prior medications.

6.2. Study Period

For the trial period discussed below, where multiple procedures are scheduled at the same nominal time point(s) relative to dosing, the following chronology of events is suggested:

1. ECGs – ECGs should be obtained prior to vital sign and blood specimen collection.

2. Blood pressure/pulse rate –obtain prior to the blood specimen collection.

3. Blood sample collection for clinical laboratories and diflunisal concentration.

4. Blood specimens for Tafamidis concentration, TTR stabilization, TTR oligomer concentration, and TTR concentration – obtain within the specified time windows.

All other procedures should be obtained after blood specimen collections, unless sampling is determined by the study personnel to potentially impact the results. For Patient Reported Outcome measures (Appendix 1), the following order should be adhered to: Kansas City Cardiomyopathy Questionnaire, (Appendix 1.1) EuroQoL-5 Dimensions, (EQ-5D-3L), (Appendix 2) and then the Patient Global Assessment (Appendix 3).

6.2.1. Baseline (Day 1)

Prior to dosing, the following procedures will be completed at the Baseline visit:

1. Review entrance criteria.

2. Randomization.

3. Medical history (updated for changes since Screening visit).

4. Brief Physical Examination with weight.

5. Single 12-lead ECG - prior to any blood pressure measurement or blood collection.

6. Vital signs (systolic and diastolic blood pressure supine and standing, pulse rate supine and standing, respiration rate, and body temperature).

7. Blood and urine sample collection for the following clinical laboratories:

    a. Hematology;

    b. Serum Chemistry;

c. Coagulation (INR, PT);

d. Retinol Binding Protein;

e. Urinalysis;

f. Urine Pregnancy test – for women of childbearing potential.

8. Collect blood sample for TTR stabilization, TTR oligomer concentration, and TTR concentration assays pre-dose.
9. Collect blood sample for diflunisal concentration (Section 7.7.3).
10. Collect Baseline pre-dose blood sample as control for tafamidis concentration.
11. Collect pharmacogenomic sample.
12. Collect blood sample for NT-proBNP and troponin I.
13. 6-Minute Walk Test (Appendix 4).
14. Kansas City Cardiomyopathy Questionnaire (Appendix 1.1).
15. EQ-5D-3L (Appendix 2).
16. Patient Global Assessment (Appendix 3).
17. NYHA classification.
18. Documentation of concomitant medications.
19. Adverse event reporting.
20. Hospitalization determination.
21. Documentation of vital status and transplant or cardiac mechanical assist device status.
22. Dispense blinded medication.

Subjects will be instructed to take their first tafamidis daily dose of 4 capsules after the completion of the Baseline procedures and to continue dosing 4 capsules each day in the morning until the next study visit.

At the end of the visit, a time will be scheduled for the Week 2 phone call along with the Month 1 appointment. The subject will be instructed not to take their medication at home on the day of the Month 1 visit, but rather wait and take the medication when instructed by the site staff when they arrive at the clinic. A Subject Daily Dosing Diary stating the date and

time of the Month 1 visit will be issued to the subject. The subject will be reminded to return to the clinic with all dispensed study medication wallets.

6.2.2. Week 2 Follow-up

1. Subjects required to have their labs drawn either at a local laboratory, at their primary physician's office or at the Investigator's site and have the samples sent to the central laboratory. The results will be sent to the investigator site. The clinical site will arrange a telephone call with the subject to inquire about any adverse effects and their health status for the Week 2 follow-up (see below).

2. Whether using the clinical site, a local laboratory or primary physician's office, the following specimens will be collected.

    a. Hematology;

    b. Serum Chemistry.

3. The site will contact the subject by phone at the time agreed with the subject at the baseline visit to collect the following information since the last visit:

    a. Documentation of concomitant medications;

    b. Adverse events reporting;

    c. Hospitalization determination;

    d. Documentation of vital status and transplant or cardiac mechanical assist device status.

At the end of the clinic visit or phone call, the Month 1 appointment will be confirmed and the subject will be reminded to take their medication in the clinic, rather than at home, on the day of the next visit, as indicated on the Subject Daily Dosing Diary. The subject will be reminded to return to the clinic with all dispensed study medication wallets.

6.2.3. Month 1 Visit

On the day of the Month 1 study visit, subjects will **NOT** take their study medication at home prior to the Month 1 clinic visit. Study medication on the day of the Month 1 visit will be taken in the clinic in order to accurately and conveniently time the tafamidis concentration blood sample, which is to be pre-dose as well as 3 hours (±1.5 hours) after the actual time of dosing.

Study site personnel will also record in the CRF the time of dosing on the day before the Month 1 visit as recorded by the subject on their Subject Daily Dosing Diary.

Prior to dosing, the following procedures will be completed at the Month 1 visit:

1. Brief physical examination with weight.
2. Single 12-lead ECG -prior to any blood collection or blood pressure measurements.
3. Vital signs (systolic and diastolic blood pressure supine and standing, pulse rate supine and standing, respiration rate, and body temperature).
4. Collect blood sample for TTR stabilization, TTR oligomer concentration, and TTR concentration assays.
5. Collect pre-dose sample for tafamidis concentrations.
6. Collect blood sample for diflunisal concentration (Section 7.7.3).

The subject is to administer the dose of blinded study medication at the clinic and the actual time of dosing will be recorded by the study site personnel.

After dosing, the following procedures will be completed:

1. Blood and urine sample collection for the following clinical laboratories:
    a. Hematology;
    b. Serum Chemistry;
    c. Coagulation (INR, PT);
    d. Retinol Binding Protein;
    e. Urinalysis;
    f. Urine pregnancy test – for women of childbearing potential.
2. Collect blood sample for TTR stabilization, TTR oligomer concentration, and TTR concentration assays at 3 hours (±1.5 hours) after dosing,
3. Collect blood sample for tafamidis concentration at 3 hours (±1.5 hours) after dosing and record the actual time of the blood sample as well as the actual time of drug dosing,
4. Documentation of concomitant medications,
5. Record dosing adherence,
6. Adverse events reporting,
7. Hospitalization determination,

8. Documentation of vital status and transplant or cardiac mechanical assist device status.

At the end of the visit the next appointment is to be scheduled and subject will be instructed to take their medication at home prior to the next visit. A Subject Daily Dosing Diary stating the date and time of the next visit will be issued to the subject. The subject will be reminded to return to the clinic with all dispensed study medications wallets.

6.2.4. Month 3 Visit

The following procedures will be completed at the Month 3 visit:

1. Brief physical examination with weight.
2. Vital Signs (systolic and diastolic blood pressure supine and standing, pulse rate supine and standing, respiration rate, and body temperature).
3. Blood sample collection for Serum Chemistry.
4. Documentation of concomitant medications.
5. Record dosing adherence.
6. Adverse event reporting.
7. Hospitalization determination.
8. Dispense blinded study medication.
9. Documentation of vital status and transplant or cardiac mechanical assist device status.

At the end of the visit, the next appointment is to be scheduled and subject will be instructed to take their medication at home prior to the next clinic visit. Visit scheduling and dosing time instructions for subjects must consider that the tafamidis concentration sample is to be collected 7 hours (± 2.5 hours) after dosing. A Subject Daily Dosing Diary stating the date and time of the next visit will be issued to the subject.

Subjects will be instructed to accurately record on the Subject Daily Dosing Diary the actual time at which they took their prior 2 doses of blinded medication at home on the day before and the day of the Month 6 visit. The subject will be reminded to return to the clinic with all dispensed study medication wallets.

6.2.5. Month 6 Visit

Subjects will take their scheduled dose at home prior to the clinic visit and record the actual time of dosing on their Subject Daily Dosing Diary. Study site personnel will record in the CRF the time of dosing the day before and the day of the Month 6 visit as recorded by the

subject on their Subject Daily Dosing Diary. Dosing at this visit should take place 7 hours (± 2.5 hours) prior to the timing of the tafamidis concentration blood collection.

The following procedures will be completed at the Month 6 visit:

1. Brief physical examination with weight.
2. Single 12-lead ECG.
3. Vital signs (systolic and diastolic blood pressure supine and standing, pulse rate supine and standing, respiration rate, and body temperature).
4. Blood and urine sample collection for the following clinical laboratories:
    a. Hematology;
    b. Serum Chemistry;
    c. Coagulation (INR, PT);
    d. Retinol Binding Protein;
    e. Urinalysis;
    f. Urine pregnancy test – for women of childbearing potential.
5. Collect blood sample for TTR stabilization, TTR oligomer concentration, and TTR concentration assays at 7 hours (± 2.5 hours) post-dose.
6. Collect blood sample for diflunisal concentration (Section 7.7.3).
7. Collect blood sample for tafamidis concentration at 7 hours (± 2.5 hours) after dosing and record the actual time of the blood sample as well as the time of drug dosing from the subject's Subject Daily Dosing Diary.
8. Echocardiogram.
9. 6-Minute Walk Test (Appendix 4).
10. Kansas City Cardiomyopathy Questionnaire (Appendix 1.1).
11. EQ-5D-3L (Appendix 2).
12. Patient Global Assessment (Appendix 3).
13. NYHA classification.
14. Documentation of concomitant medications.

15. Record dosing adherence.

16. Adverse event reporting.

17. Hospitalization determination.

18. Dispense blinded study medication.

19. Documentation of vital status and transplant or cardiac mechanical assist device status.

At the end of the visit the next appointment is to be scheduled. A Subject Daily Dosing Diary stating the date and time of the next visit will be issued to the subject. The subject will be reminded to return to the clinic with all dispensed study medication wallets.

6.2.6. Month 9 Visit

The following evaluations will be performed for all subjects at the Month 9 visit.

1. Brief physical examination with weight.

2. Vital signs (systolic and diastolic blood pressure supine and standing, pulse rate supine and standing, respiration rate, and body temperature).

3. Blood sample collection for Serum Chemistry.

4. Documentation of concomitant medications.

5. Record dosing adherence.

6. Adverse event reporting.

7. Hospitalization determination.

8. Dispense blinded study medication.

9. Documentation of vital status and transplant or cardiac mechanical assist device status.

At the end of the visit, the next appointment is to be scheduled and subject will be instructed to take their medication at home prior to the next clinic visit. Visit scheduling and dosing time instructions for subjects must consider that the tafamidis concentration sample is to be collected 7 hours (± 2.5 hours) after dosing. A Subject Daily Dosing Diary stating the date and time of the next visit will be issued to the subject. Subjects will be instructed to accurately record on the Subject Daily Dosing Diary the actual time at which they took their prior 2 doses of blinded medication at home on the day before and the day of the Month 12 visit. The subject will be reminded to return to the clinic with all dispensed study medication wallets.

6.2.7. Month 12 Visit

Subjects will take their scheduled dose at home prior to the clinic visit and record the actual time of dosing on their Subject Daily Dosing Diary. Study site personnel will record in the CRF the time of dosing the day before and the day of the Month 12 visit as recorded by the subject on their Subject Daily Dosing Diary. Dosing at this visit should take place 7 hours (± 2.5 hours) prior to the timing of the tafamidis concentration blood collection.

The following procedures will be completed at the Month 12 visit:

1. Brief physical examination with weight.
2. 12-Lead ECG.
3. Vital signs (systolic and diastolic blood pressure supine and standing, pulse rate supine and standing, respiration rate, and body temperature).
4. Blood and urine sample collection for the following clinical laboratories:
    a. Hematology;
    b. Serum Chemistry;
    c. Coagulation (INR, PT);
    d. Retinol Binding Protein;
    e. Urinalysis;
    f. Urine pregnancy test – for women of childbearing potential.
5. Collect blood sample for TTR stabilization, TTR oligomer concentration, and TTR concentration assays at 7 hours (± 2.5 hours) post-dose.
6. Collect blood sample for tafamidis concentration at 7 hours (± 2.5 hours) after dosing and record the actual time of the blood sample as well as the time of drug dosing from the subject's Subject Daily Dosing Diary.
7. At selected centers only, collect urine sample for assay development of TTR oligomer concentration.
8. Collect blood sample for NT-proBNP and troponin I.
9. 6-Minute Walk Test.
10. Kansas City Cardiomyopathy Questionnaire (Appendix 1.1).
11. EQ-5d-3L (Appendix 2).

12. Patient Global Assessment (Appendix 3).
13. NYHA classification.
14. Documentation of concomitant medications.
15. Record dosing adherence.
16. Adverse event reporting.
17. Hospitalization determination.
18. Dispense blinded study medication.
19. Documentation of vital status and transplant or cardiac mechanical assist device status.

At the end of the visit the next appointment is to be scheduled. A Subject Daily Dosing Diary stating the date and time of the next visit will be issued to the subject. The subject will be reminded to return to the clinic with all dispensed study medication wallets.

6.2.8. Month 15 Visit

The following evaluations will be performed for all subjects at the Month 15 visit:

1. Brief physical examination with weight.
2. Vital signs (systolic and diastolic blood pressure supine and standing, pulse rate supine and standing, respiration rate and body temperature).
3. Blood sample collection for Serum Chemistry.
4. Documentation of concomitant medications.
5. Record dosing adherence.
6. Adverse event reporting.
7. Hospitalization determination.
8. Dispense blinded study medication.
9. Documentation of vital status and transplant or cardiac mechanical assist device status.

At the end of the visit, the next appointment is to be scheduled and subject will be instructed to take their medication in the clinic, rather than at home, on the day of the next visit. A Subject Daily Dosing Diary stating the date and time of the next visit will be issued to the subject. Subjects will be instructed to accurately record on the Subject Daily Dosing Diary the actual time at which they took their dose of blinded medication at home on the day before the Month 18 visit. The subject will be reminded to return to the clinic with all dispensed study medication wallets.

6.2.9. Month 18 Visit

On the day of the Month 18 study visit, subjects will **NOT** take their study medication at home prior to the Month 18 clinic visit. Study medication on the day of the Month 18 visit will be taken in the clinic in order to accurately and conveniently time the tafamidis concentration blood sample, which is to be 1 hour (± 30 minutes) after the actual time of dosing.

Study site personnel will also record in the CRF the time of dosing on the day before the Month 18 visit as recorded by the subject on their Subject Daily Dosing Diary.

After dosing, the following procedures will be completed at the Month 18 visit:

1. Brief physical examination with weight.
2. Single 12-Lead ECG.
3. Vital signs (systolic and diastolic blood pressure supine and standing, pulse rate supine and standing, respiration rate, and body temperature).
4. Echocardiogram.
5. Blood and urine sample collection for the following clinical laboratories:
    a. Hematology;
    b. Serum Chemistry;
    c. Coagulation (INR, PT);
    d. Retinol Binding Protein;
    e. Urinalysis;
    f. Urine pregnancy test – for women of childbearing potential.
6. Collect blood sample for TTR stabilization, TTR oligomer concentration, and TTR concentration assays at 1 hr (± 30 minutes) post-dose.

7. Collect blood sample for tafamidis concentration at 1 hour (± 30 minutes) after dosing and record the actual time of the blood sample as well as the actual time of drug dosing.

8. At selected centers only, collect urine sample for assay development of TTR oligomer concentration.

9. Collect blood sample for diflunisal concentration (Section 7.7.3).

10. 6-Minute Walk Test (Appendix 4).

11. Kansas City Cardiomyopathy Questionnaire (Appendix 1.1).

12. EQ-5D-3L (Appendix 2).

13. Patient Global Assessment (Appendix 3).

14. NYHA classification.

15. Documentation of concomitant medications.

16. Record dosing adherence.

17. Adverse event reporting.

18. Hospitalization determination.

19. Dispense blinded study medication.

20. Documentation of vital status and transplant or cardiac mechanical assist device status.

At the end of the visit, the next appointment is to be scheduled. A Subject Daily Dosing Diary stating the date and time of the next visit will be issued to the subject. The subject will be reminded to return to the clinic with all dispensed study medication wallets.

6.2.10. Month 21 Visit

The following procedures will be performed for all subjects at the Month 21 visit:

1. Brief physical examination with weight.

2. Vital signs (systolic and diastolic blood pressure supine and standing, pulse rate supine and standing, respiration rate, and body temperature).

3. Blood sample collection for Serum Chemistry.

4. Documentation of concomitant medications.

5. Record dosing adherence.

6. Adverse event reporting.

7. Hospitalization determination.

8. Dispense blinded study medication.

9. Documentation of vital status and transplant or cardiac mechanical assist device status.

At the end of the visit, the next appointment is to be scheduled and subject will be instructed to take their medication in the clinic, rather than at home, on the day of the next visit. A Subject Daily Dosing Diary stating the date and time of the next visit will be issued to the subject. Subjects will be instructed to accurately record on the Subject Daily Dosing Diary the actual time at which they took their dose of blinded medication at home on the day before the Month 24 visit. The subject will be reminded to return to the clinic with all dispensed study medication wallets.

6.2.11. Month 24 Visit

On the day of the Month 24 study visit, subjects will **NOT** take their study medication at home prior to the Month 24 clinic visit. Study medication on the day of the Month 24 visit will be taken in the clinic in order to accurately and conveniently time the tafamidis concentration blood sample, which is to be 1 hour (± 30 minutes) after the actual time of dosing.

Study site personnel will also record in the CRF the time of dosing on the day before the Month 24 visit as recorded by the subject on their Subject Daily Dosing Diary.

After dosing, the following procedures will be completed at the Month 24 visit:

1. Brief physical examination with weight.

2. Single 12-Lead ECG.

3. Vital signs (systolic and diastolic blood pressure supine and standing, pulse rate supine and standing, respiration rate, and body temperature).

4. Blood and urine sample collection for the following clinical laboratories.

    a. Hematology;

    b. Serum Chemistry;

    c. Coagulation (INR, PT);

    d. Retinol Binding Protein;

e. Urinalysis;

f. Urine pregnancy test – for women of childbearing potential.

5. Collect blood sample for TTR stabilization, TTR oligomer concentration, and TTR concentration assays at 1 hour (± 30 minutes) post-dose.

6. Collect blood sample for tafamidis concentration at 1 hour (± 30 minutes) after dosing and record the actual time of the blood sample as well as the actual time of drug dosing.

7. At selected centers only, collect urine sample for assay development of TTR oligomer concentration.

8. .6-Minute Walk Test (Appendix 4).

9. Kansas City Cardiomyopathy Questionnaire (Appendix 1.1).

10. EQ-5D-3L (Appendix 2).

11. Patient Global Assessment (Appendix 3).

12. NYHA classification.

13. Documentation of concomitant medications.

14. Record dosing adherence.

15. Adverse event reporting.

16. Hospitalization determination.

17. Dispense blinded study medication.

18. Documentation of vital status and transplant or cardiac mechanical assist device status.

At the end of the visit, the next appointment is to be scheduled. A Subject Daily Dosing Diary stating the date and time of the next visit will be issued to the subject. The subject will be reminded to return to the clinic with all dispensed study medication wallets.

6.2.12. Month 27 Visit

The following procedures will be performed for all subjects at the Month 27 visit:

1. Brief physical examination with weight.

2. Vital signs (systolic and diastolic blood pressure supine and standing, pulse rate supine and standing, respiration rate, and body temperature).

3. Blood sample collection for Serum Chemistry.

4. Documentation of concomitant medications.

5. Record dosing adherence.

6. Adverse event reporting.

7. Hospitalization determination.

8. Dispense blinded study medication.

9. Documentation of vital status and transplant or cardiac mechanical assist device status.

At the end of the visit, the next appointment is to be scheduled and subject will be instructed to take their medication at home prior to the next clinic visit. A Subject Daily Dosing Diary stating the date and time of the next visit will be issued to the subject. Subjects will be instructed to accurately record on the Subject Daily Dosing Diary the actual time at which they took their dose of blinded medication at home on the day before and the day of the Month 30 visit. The subject will be reminded to return to the clinic with all dispensed study medication wallets.

6.2.13. Month 30 Visit or Early Study Discontinuation

Subjects will take their scheduled dose at home on the day of the clinic visit and record the actual times of dosing for the 2 doses prior to the visit on their Subject Daily Dosing Diary. Study site personnel will record in the CRF the time of dosing the time of dosing the day before and the day of the Month 30 visit as recorded by the subject on their Subject Daily Dosing Diary. The following procedures will be performed for all subjects at the Month 30 visit or at the time of Early Study Discontinuation:

1. Full physical examination with weight.

2. Single 12-Lead ECG.

3. Vital signs (systolic and diastolic blood pressure supine and standing, pulse rate supine and standing, respiration rate, and body temperature).

4. Echocardiogram.

5. Blood and urine sample collection for the following clinical laboratories:

    a. Hematology;

b. Serum Chemistry;

c. Coagulation (INR, PT);

d. Retinol Binding Protein;

e. Urinalysis;

f. Urine pregnancy test – for women of childbearing potential.

6. Collect blood sample for TTR stabilization, TTR oligomer concentration, and TTR concentration assays at any time during the clinic visit.

7. Collect blood sample for tafamidis concentration at any time after dosing and record the actual time of the blood sample as well as the time of drug dosing from the subject's Subject Daily Dosing Diary.

8. At selected centers only, collect urine sample for assay development of TTR oligomer concentration.

9. Collect blood sample for NT-proBNP and troponin I.

10. Collect blood sample for diflunisal concentration (Section 7.7.3).

11. 6-Minute Walk Test (Appendix 4).

12. Kansas City Cardiomyopathy Questionnaire (Appendix 1.1).

13. EQ-5D-3L (Appendix 2).

14. Patient Global Assessment (Appendix 3).

15. NYHA classification.

16. Documentation of concomitant medications.

17. Record dosing adherence.

18. Adverse event reporting.

19. Hospitalization determination.

20. Documentation of vital status, transplant or cardiac mechanical assist device status (within 2 weeks of the target Month 30 visit).

Additionally, except for subjects who are randomized into the extension study (Study B3461045), subjects will have a 4-week (28 calendar days) safety follow-up visit after the last dose of the study medication for collection of adverse events. This visit can be completed by telephone.

6.2.14. Dialysis or Hemofiltration Treatments and Tafamidis Concentrations

Should a subject require dialysis or hemofiltration at any time after randomization while on study treatment, the subject should have blood samples collected for tafamidis concentrations around the time of renal replacement therapy. The timing of the sample collection will depend on the type of renal replacement therapy administered. For hemodialysis or hemofiltration, samples should be collected on the date of the renal replacement therapy both prior to administration and after administration. When peritoneal dialysis is administered, the first sample should be collected at initiation of the first exchange. The second sample should be collected after the first exchange is completed (if performed outside of the home) or at least 24 hours after the initiation of the first exchange (if administered at home). Every effort should be made to collect these samples on the date of the subject's first administration of renal replacement therapy in the study; however, if this is not possible, the samples should be obtained as soon as possible on the date of a renal replacement therapy treatment. If necessary, the sample collection can be obtained using the guidelines for lab sample collection in the Guidance for Remotely Conducted Study Visits provided for the study. At the time of sample collection, the date and time of the last dose and the date and time of sample collection must be recorded.

6.3. Subject Withdrawal and Vital Status / Transplant / Cardiac Mechanical Assist Device Status Follow-up

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol required schedule of study visits or procedures at a given study site.

Due to the inclusion of all-cause mortality in the primary analysis, a Release of Medical Information Form will be required of all subjects for the purpose of access to medical records as well as for obtaining vital status / transplant / cardiac mechanical assist device status follow-up with the subject's primary physician or with death registries. The signing of this Release of Medical Information Form is in addition to the Informed Consent Document. In some cases, sites may combine these two forms into a single form, as is their standard practice.

In the situation where the subject or the alternative designated contact (ie, individual identified in the Release of Medical Information Form) cannot be reached, attempts will be made to ascertain the vital status / transplant / cardiac mechanical assist device status of the subject by searching the appropriate national or regional vital status registry or other relevant databases, where available and allowable by local law. Depending on the local law, this search will be conducted by the enrolling physician, his/her designee at the study site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. The site should make a minimum of 3 documented phone calls followed by a registered letter inquiring about the reason for lack of return for the scheduled appointment. In any circumstance, every effort should be made to document subject outcome, if possible, including the subject's vital status / transplant / cardiac mechanical assist device status through 30 months following the Baseline visit. The investigator should inquire about the reason for withdrawal, request that the subject return for a final study visit (if applicable) and return all unused investigational product(s), and follow-up with the subject regarding any unresolved adverse events (AEs).

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected, except for ascertaining vital status / transplant / cardiac mechanical assist device status at 30 months after Baseline. The sponsor may retain and continue to use any data collected before such withdrawal of consent. Subjects requesting withdrawal should be informed that withdrawal of consent for follow-up will jeopardize the public health value of the study. At the time of withdrawal, subjects will be asked about the contribution of possible adverse events to their decision to withdraw consent and any adverse event information elicited will be documented. Preferably the subject should withdraw consent in writing and, if the subject or the subject's representative refuses or is physically unavailable, the site should document and sign the reason for the subject's failure to withdraw consent in writing.

6.3.1. Subject Withdrawal for Heart or Liver Transplantation or Implantation of Cardiac Mechanical Assist Device

Subjects may be on a transplant list at the time of randomization. However, if a subject chooses to accept a donor organ transplant during the study or undergoes implantation of a cardiac mechanical assist device, they will stop taking blinded study medication and be discontinued from study participation prior to the transplant operation. Vital status / transplant status for the subject will be established through 30 months (910 days) following the Baseline visit. Subjects who discontinue from the study due to transplantation or implantation of a cardiac mechanical assist device will be handled in the statistical analysis as described in Section 9.2.1.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However, it is anticipated, that from time to time there may be circumstances, outside of the control of the investigator that may make it unfeasible to perform assessments as planned. In these cases, the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol required assessment cannot be performed, the investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to, as soon as possible. The study team will be informed of these incidents in a timely fashion.

All visits will be scheduled from the Baseline visit on Day 1, so that study participation will be for 30 months. In the event that an actual clinic visit day differs from the scheduled clinic visit day, the next visit will be scheduled according to the original timing relative to Baseline so that the study schedule is maintained.

7.1. Biopsy Documentation of Amyloid Deposition

In the event that there is no documentation of prior biopsy and demonstration of TTR amyloid deposition by either mass spectrometry, immunohistochemistry or scintigraphy [See Section 4.1], cardiac or non-cardiac tissue will be biopsied and tested by the investigational site as per the site's standard of care and evaluated with Congo red stain or alcian blue stain. Stained tissue will be viewed under polarized light used to demonstrate amyloid characteristic 'apple-green' birefringence. For subjects without identification of a TTR variant and demonstration of amyloid deposition who may have a diagnosis of wild-type TTR-CM (SSA), analysis will be performed to confirm the precursor protein basis for amyloid deposition, by either: mass spectrometry, immunohistochemistry or scintigraphy [see Section 4.1].

7.2. TTR Genotyping

Subjects with a documented prior genotyping and the original laboratory result or copy for source documentation will not require additional genotyping. Subjects without prior genotyping will require collection of a blood sample for TTR genotype testing. The sample will be sent to a reference laboratory for complete genomic sequencing.

Complete information on sample collection, storage, and sample transport for genotype confirmation are detailed in a separate laboratory manual.

7.3. Renal Function Assessment

Renal function will be assessed using the modified Modification of Diet in Renal Disease (MDRD) equation for estimated glomerular filtration rate (eGFR).

eGFR (mL/min/1.73 m^2) = 175 x $(S_{cr})^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.212 if African-American) [from http://nkdep.nih.gov/lab-evaluation/gfr/estimating.shtml].

7.4. Modified Body Mass Index

Transthyretin, in the monomeric form, can enter cardiac and neural tissues. As part of the polyneuropathy, TTR can cause severe gastrointestinal problems resulting in wasting. A means of determining if there is gastrointestinal involvement in subjects is to calculate their mBMI. Body Mass Index (BMI) is calculated as weight (kg) / [height (meters)]^2. The mBMI is calculated by multiplying BMI by serum albumin concentration (g/L).

7.5. Pharmacogenomic Biomarker

7.5.1. Markers of Drug Response

Variation in genetic markers and other biomarkers may help to explain some of the variability in response seen with some drugs among different individuals. This is referred to as pharmacogenomic/biomarker research. Comparing the DNA, RNA, protein, and metabolite variation patterns of subjects who respond well and those who respond poorly to treatment may help to better define the most appropriate group of patients in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/biomarker analyses and retaining them in the Pfizer BioBank makes it possible to better understand the drug's mechanism of action and to seek explanations for differences in, for example, exposure, efficacy, tolerability, or safety not anticipated prior to the beginning of the study. Providing these biospecimens is a required study activity for study sites and subjects, unless prohibited as such by local regulations or ethics committee decision.

To protect subjects' confidentiality, the banked biospecimens and data generated from them will be coded with the subject's study ID number. Samples will be kept in a facility accessible only by badge-swipe. Data will be stored on password-protected computer systems. The key between the code and the subject's personal identifiers will be held at the study site; the researchers using the biospecimens and data generated from them will not have access to the key nor any personally identifying information. Biospecimens will only be used for the purposes described here and in the informed consent document/patient information sheet; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored indefinitely to allow for future research on the topics described here, including research conducted during the lengthy drug development process and also post-marketing research. Subjects can withdraw their consent for the use of their biospecimens at any time by making a request to the investigator, in which event any remaining biospecimen will be destroyed; data already generated from the biospecimens will continue to be stored to protect the integrity of existing analyses. It is very unlikely that results generated from the biospecimens will have any clinical, diagnostic, or therapeutic implications for the individual study participants. Subjects are notified in the informed consent document/patient information sheet that their results will not be given to them, unless required by local laws or regulations, in which case results will be returned via the investigator. Results will not be provided to family members or other physicians; nor will they be recorded in the subject's medical record. There is no intention to contact subjects after completion of the clinical trial.

A blood biospecimen **Prep D1 (K_2 EDTA whole blood collection optimized for DNA analysis)** will be collected at the Baseline visit to be retained for potential pharmacogenomic/biomarker analyses related to drug response, unless prohibited by local regulations or ethics committee decision. Putative safety biomarkers, drug metabolizing enzyme genes, drug transport protein genes, or genes thought to be related to the mechanism of drug action may be examined.

The Banked Biospecimens will be collected from all subjects **unless prohibited by local regulations or ethics committee decision**. Detailed collection, processing, storage and shipment instructions are provided in the central laboratory manual.

It is possible that the use of these biospecimens may result in commercially viable products. Subjects will be advised in the informed consent document/patient information sheet that they will not be compensated in this event.

7.5.2. Additional Research

Unless prohibited by local regulations, subjects will be asked to indicate on a consent form whether they will allow the Banked Biospecimens to also be used for the following research:

- Investigations of the disease under study in the clinical trial, and related conditions,
- Biospecimens may be used as controls. This includes use in case-control studies of diseases for which Pfizer is researching drug therapies; use in characterizing the natural variation amongst people in genes, RNA, proteins, and metabolites; and use in developing new technologies related to Pharmacogenomics/biomarkers.

Subjects need not provide additional biospecimens for the uses described in this section; the biospecimens specified in Section 7.5.1 will be used. Subjects may still participate in the clinical trial if they elect not to allow their Banked Biospecimens to be used for the additional purposes described in this section.

7.6. Safety Assessments

7.6.1. Medical History

A complete medical history is to be documented for all subjects during the Screening Period. This medical history will document the specific symptoms the subject reports associated with TTR-CM, as well as any additional co-morbid conditions or symptoms. Medical history will be updated at the Baseline visit for changes since the Screening visit.

7.6.2. Physical Examinations and Height and Weight Measurements

All subjects will undergo a physical examination during the Screening Period and the Month 30 visit or Early Study Discontinuation, including assessment of the following body systems:

General appearance
Head and neck
Eyes
Ears
Nose
Throat
Genitourinary
Neurological
Cardiovascular
Abdomen
Skin
Musculoskeletal
Respiratory

Brief physical examinations, including assessment of general appearance, cardiovascular, respiratory, and gastrointestinal system, are to be performed at all other study visits.

Measurement of height in centimeters (cm) will be collected at the Screening visit only. Weight in kilograms (kg) will be collected at each study clinic visit.

7.6.3. Vital Signs

Vital signs will be recorded at each study visit.

Supine and standing blood pressure will be measured with the subject's arm supported at the level of the heart, and recorded to the nearest mm Hg. The same arm (preferably the dominant arm) will be used throughout the trial. The subject should be supine for at least 3 minutes before the supine blood pressure is obtained. Standing blood pressure should then be measured approximately 2 minutes after the subject assumes the standing position. The same size blood pressure cuff, which has been properly calibrated, will be used to measure blood pressure at each time point. The use of automated devices for measuring BP and pulse rate are acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, blood pressure and pulse rate should be obtained prior to the nominal time of the blood collection.

7.6.4. Electrocardiograms

A 12-lead electrocardiogram (ECG) will be performed for all subjects at Screening, Baseline, Months 1, 6, 12, 18, 24, and 30. Where possible, ECGs will be performed before blood pressure or pulse measurements or blood collection. For ECG recordings, the subjects will remain supine for about 5 minutes before recording the ECG.

The following ECG parameters will be assessed: PR, RR, QRS, QT, and QTc (B and F) interval, heart rate, and overall interpretation, with recording of any abnormal findings. Ten-second rhythm strips will accompany each ECG. For subject entry into the study, each ECG will be recorded and read locally by the clinical site, and the clinical significance of ECG findings will be assessed by the investigator.

In addition, for overall analysis of the ECG parameters, each ECG will be digitalized and sent to an independent ECG laboratory that will conduct a centralized review of the results for confirmation by an independent cardiologist.

Detailed instructions for performing ECGs are provided in a separate study laboratory manual (Centralized ECG Procedure Manual).

7.6.5. Echocardiograms

Echocardiography (2D Doppler) will be performed for all subjects at Screening and Months 6, 18, and 30 (or Early Study Discontinuation). The assessment of end-diastolic interventricular septal thickness for study entry will be based on the echocardiogram performed at the Screening visit as interpreted by the independent central laboratory. If the Screening echocardiographic recording is not clear enough to accurately determine the end-diastolic interventricular septal wall thickness, it must be repeated. Each echocardiogram will be recorded and reviewed locally by the clinical site, and the clinical

significance of echocardiogram findings will be assessed by the Investigator. Each echocardiogram will also be sent to an independent central laboratory that will conduct a centralized review of the results. The central reading of the Screening echocardiogram must be completed prior to subject randomization at the Baseline visit.

The following parameters will be included in the assessment:

1. End-diastolic interventricular septal wall thickness (mm).
2. Left ventricle posterior wall thickness (mm).
3. Left ventricular ejection fraction (%).
4. Left ventricular stroke volume (mL).
5. Fractional shortening (%).
6. Left atrial diameter, anterior-posterior (mm).
7. Left atrial diameter, medio-lateral (mm).
8. Left atrial diameter, superior-inferior (mm).
9. Left ventricular end systolic diameter (mm).
10. Left ventricular end systolic volume (mL).
11. Left ventricular end-diastolic diameter (mm).
12. Left ventricular end-diastolic volume (mL).
13. Left ventricular mass (g).
14. E/A Ratio.
15. E/E' Ratio.
16. Global longitudinal strain.
    a. Basal septal;
    b. Mid septal;
    c. Apical septal;
    d. Basal lateral;
    e. Mid lateral;

f. Apical lateral.

17. Circumferential strain basal global.

18. Circumferential strain mid global.

19. Circumferential strain apical global.

20. Radial strain basal global.

21. Radial strain mid global,

22. Radial strain apical global.

Detailed instructions for performing echocardiography are provided in a separate study laboratory manual (Echocardiography Imaging Manual).

7.6.6. Clinical Laboratory Tests

Blood and urine samples will be collected at Screening, Baseline, Week 2 (no urine), and at Months 1, 6, 12, 18, 24, and 30 as well as in the event of Early Study Discontinuation. Serum chemistry will be collected at each study visit.

The following clinical laboratory parameters will be assessed:

Serum Chemistry		
Sodium	Inorganic Phosphorus	Aspartate aminotransferase (AST)
Potassium	Glucose	Gamma glutamyl transferase
Chloride	Total bilirubin	Cholesterol
Bicarbonate	Total protein	Uric acid
Blood Urea Nitrogen	Albumin	Thyroid-stimulating hormone
Creatinine	Globulin	Total thyroxine (T4)
Calcium	Alanine aminotransferase (ALT)	Free T4
Retinol binding protein		Alkaline Phosphatase

Coagulation (to be measured in site's local laboratory)	
International normalized ratio (INR)	Prothrombin time (PT)

Hematology	
Hemoglobin	White blood cell count
Hematocrit	Neutrophils
Red blood cell count	Lymphocytes
Mean corpuscular volume	Monocytes

Mean corpuscular hemoglobin	Eosinophils
Mean corpuscular hemoglobin concentration	Basophils
Platelets	

Urinalysis	
pH	Blood (free Hb)
Protein	Nitrite
Glucose	Urobilinogen
Ketones	Specific gravity
Bilirubin	

Urinalysis will be a qualitative determination by dipstick at the site. If the urine dipstick demonstrates a positive result for any test, the specimen will be sent to the Central Laboratory for microscopic evaluation.

Specifications for sample collection are provided in the study laboratory manual.

7.6.7. Pregnancy Testing

For female subjects of childbearing potential, a urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at the Screening and Baseline visits before investigational product administration and at the end of treatment visit. A negative pregnancy result is required before the subject may receive the investigational product. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected), repeated at and Months 1, 6, 12, 18, 24, and 30 (or Early Study Discontinuation) to confirm that the subject has not become pregnant during the study. In the case of a positive hCG test, the subject will be discontinued from the study. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.

7.6.8. Testing for Light Chain Amyloid

Specifications for testing samples are provided in the study laboratory manual.

Elderly subjects with reduced renal function may experience elevations in levels of free kappa light chains and free lambda light chains with no change in the kappa/lambda ratio. Subjects with elevated serum / urine levels of free kappa light chain, free lambda light chain and a free kappa / lambda ratio indicative of light chain amyloidosis (MGUS) will require confirmatory test using mass spectrometry or immunohistochemistry with electron microscopy or scintigraphy [See Section 4.1].

7.6.9. N-Terminal Prohormone of Brain Natriuretic Peptide (NT-proBNP) and Troponin I

Specifications for sample collection can be found in the study laboratory manual.

7.6.10. Serology

All subjects will be tested for hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (anti-HCV), and human immunodeficiency virus (HIV) during the Screening period. Subjects with positive findings on these serologies will be excluded from study participation.

7.7. Efficacy Assessments

7.7.1. Patient Reported Outcomes

Sites will be provided with an approved translated version of each questionnaire that will be required for use in the study.

7.7.1.1. Kansas City Cardiomyopathy Questionnaire

The KCCQ (Appendix 1.1) (Green 2000)[19] is a 23-item subject-completed questionnaire that assesses health status and health-related quality of life in subjects with heart failure. Items assess the ability to perform activities of daily living, frequency and severity of symptoms, the impact of these symptoms, and health-related quality of life. Response options vary by question. Scoring yields scores for 6 domains (Physical limitation, Symptom stability, Symptoms, Self-efficacy, Social limitation, and Quality of life), two summary scores (Functional summary and Clinical summary), as well as an Overall Summary score. Domain scores are transformed to a 0 to 100 range; higher scores indicate better health status. It takes approximately 4-6 minutes for a subject to complete the KCCQ.

Subjects will complete the KCCQ at the Baseline visit and at Months 6, 12, 18, 24, and 30 (or Early Study Discontinuation) as listed in the Schedule of Activities. In each instance of administration, the KCCQ should be completed by subjects before completing the EQ-5D-3L (Appendix 2) and PGA assessments(Appendix 3).

The KCCQ can be found in Section Appendix 1.1.

7.7.1.2. EQ-5D-3L

The EQ-5D-3L Appendix 2 (3 levels version) is a brief, self-administered generic health status instrument that takes about 5 minutes to complete (Euroqol Group 1990).[14] The instrument consists of two parts. In the first part, respondents are asked to rate their current health state on 5 dimensions (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) with each dimension having three levels of function (1=no problem, 2=some problem, and 3=extreme problem). The second part is a subject's self-rating of current health state on a Visual Analog Scale (EQ-5D VAS) with endpoints labeled 'best imaginable health state' (score of 100) and 'worst imaginable health state' (score of 0). The scores from the 5 dimensions may be used to calculate a single index value, also known as a utility score.

Subjects will complete the EQ-5D-3L (Appendix 2) at the Baseline visit and at visit Months 6, 12, 18, 24, and 30 (or Early Study Discontinuation) as listed in the Schedule of Activities. Subjects should complete the EQ-5D-3L after the KCCQ (Appendix 1.1).

The EQ-5D-3L can be found in (Appendix 2).

7.7.1.3. Patient Global Assessment (PGA)

The subject's overall health status will be assessed by the PGA. At Baseline, subjects will be asked to rate their current health on the PGA using seven response options that range from "Normal, not at all ill" to "Among the most extremely ill". At follow-up visits subjects will be asked to rate the change in their health status since Baseline.

Subjects will complete the PGA at the Baseline visit and at Months 6, 12, 18, 24, and 30 (or Early Study Discontinuation) as listed in the Schedule of Activities. Subjects should complete the PGA after the KCCQ (Appendix 1.1) and EQ-5D-3L (Appendix 2).

The PGA can be found in Section Appendix 3.

7.7.2. TTR Stabilization, TTR Oligomer Concentration, and TTR Concentration Measurements

One (1) whole blood sample will be collected at Baseline and Months 1, 6, 12, 18, 24, and 30 (or Early Study Discontinuation) at times of sampling for tafamidis concentration, to test for stabilization of TTR and TTR concentration. These samples will be analyzed using validated analytical methods in compliance with Pfizer standard operating procedures. Detailed instructions for collection, storage, labeling, and shipment of all samples are provided in a separate study laboratory manual.

These samples may also be used to validate and implement an assay to measure TTR oligomer concentration. Subjects at selected centers will be asked to provide a urine sample to be used in assay development for measurement of TTR oligomer concentrations in urine. For those subjects who provide consent, a 10 mL aliquot of urine will be collected (starting at the earliest possible prospective visit for the subject) at Months 12, 18, 24, and 30 (or Early Study Discontinuation); this aliquot will be obtained from the urine sample already collected for urinalysis at these visits.

Additional instructions for collection, storage, labeling, and shipment of all samples are provided in the study laboratory manual.

7.7.3. Diflunisal Concentration

After the recording of ECGs, Echocardiograms and blood pressure, a blood sample will be collected to determine if the subject has taken diflunisal. The blood sample for this assessment will be taken at Screening, Baseline and Months 1, 6, 18, and 30. Use of diflunisal during the study is not permitted. Subjects taking diflunisal will be appropriately counselled. Such subjects will be handled as protocol violators in the analysis as described in the Statistical Analysis Plan.

Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.

Detailed instructions for collection, storage, labeling, and shipment of all samples are provided in a separate study laboratory manual.

7.7.4. 6-Minute Walk Test (6MWT)

A 6MWT will be conducted during the Screening period and at the Baseline visit and at Month 6, 12, 18, 24, and 30 visits (or Early Study Discontinuation). There will be one 6MWT during the Screening period. Subjects who are unable to walk 100 meters at Screening will be considered a Screen Failure.

The test will be conducted in accordance with guidelines established by the American Thoracic Society.

Detailed instructions for conducting the 6MWT are provided in Section Appendix 4.

7.7.5. New York Heart Association Classification

Subjects will be evaluated using the New York Heart Association (NYHA) classification at Screening, Baseline, and at Month 6, 12, 18, 24, and 30.

New York Heart Association (NYHA) Classification:

Class I

Subjects with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.

Class II

Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina pain.

Class III

Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.

Class IV

Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

7.7.6. Pharmacokinetic Measurements

Pharmacokinetic samples, to determine the tafamidis concentration, will be collected at Baseline (pre-dosing) and at Months 1, 6, 12, 18, 24, and 30 (or Early Study Discontinuation). For the Month 1, 18, and 24 visits, subjects will be instructed to not take their daily dose at home but rather to bring the dose to the clinic and they will be instructed at the clinic when to take their dose. Subjects will be instructed by clinic staff when to take their dose prior to arriving for the clinic visit at Months 6 and 12. The dosing time provided to each subject for each visit should be timed such that the tafamidis concentration sampling time occurs during the clinic visit. This determination must consider travel time to clinic and other procedures to be performed at that visit. It is imperative that the actual clock time of dosing on the specified days and the actual clock time of tafamidis concentration sample collection on the day of each clinic visit is recorded.

1. At the Baseline (Day 1) visit, tafamidis concentration samples will be collected pre-dose.

2. At Month 1, a tafamidis concentration sample will be collected pre-dose and at 3 hours (± 1.5 hours) post-dose.

3. At Month 6, a tafamidis concentration samples will be collected at 7 hours (± 2.5 hours) post-dose.

4. At Month 12, a tafamidis concentration sample will be collected at 7 hours (± 2.5 hours) post-dose.

5. At Month 18, a tafamidis concentration sample will be collected at 1 hour (± 30 minutes) post-dose.

6. At Month 24, a tafamidis concentration sample will be collected at 1 hour (±30 minutes) post-dose.

7. At Month 30 (or Early Study Discontinuation), a tafamidis concentration sample can be taken at any time during the clinic visit and the actual time of dosing and sample collection will be recorded.

In addition, should a subject require dialysis at any time after randomization while on study treatment, the subject should have blood samples collected for tafamidis concentrations on the date of dialysis both prior to dialysis and after dialysis. Every effort should be made to collect these samples on the date of the subject's first dialysis treatment in the study; however, if this is not possible, the samples should be obtained as soon as possible on the date of a dialysis treatment. If necessary, the sample collection can be obtained using the guidelines for lab sample collection in the remote visit guide for the study. At the time of sample collection, the date and time of the last dose and the date and time of sample collection will be noted.

Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures. Detailed instructions for collection, storage, labeling, and shipment of all samples are provided in a separate study laboratory manual.

As part of understanding the pharmacokinetics of the study drug, samples may be used for metabolite identification and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the clinical report. Samples collected for this purpose will be retained in accordance to local regulations and if not used within this timeframe, will be destroyed.

Detailed instructions for storage, labeling, and shipment of all samples are provided in a separate study laboratory manual.

7.8. Hospitalization Determination

Sites will determine at each visit whether the subject has been hospitalized (including the reason for hospitalization). -

Hospitalization for endpoint adjudication is defined as a non-elective admission to an acute care setting for medical therapy that results in at least a 24-hour stay (or a date change if the time of admission/discharge is not available). Cardiovascular-related hospitalization includes hospitalizations with a discharge diagnosis that includes a cardiovascular reason for hospitalization.

Hospitalization does not include admission to the following:

1. Rehabilitation facilities.
2. Hospice facilities.
3. Respite care (eg, caregiver relief).
4. Skilled nursing facilities.
5. Nursing homes.
6. Routine emergency room admissions (less than 24 hours).
7. Same-day surgeries (as outpatient/same-day/ambulatory procedures).

The Investigator is responsible for:

1. Ensuring potential study endpoints, including dates of admission and dates of discharge, are documented in the source documents.
2. Providing access to source documentation that supports the study endpoints (eg, hospital discharge summaries, procedure summaries, death certificates, and autopsy reports).

In addition, for the variables All-Cause Days Hospitalized and Cardiovascular-related Days Hospitalized, the cumulative duration of hospitalized days for an entire hospitalization will be utilized. For Cardiovascular-related Days Hospitalized, cardiovascular relatedness for the cause of hospitalization will be adjudicated and subsequently, all of the days of that hospitalization will be considered to be cardiovascular-related days hospitalized. Specifically, within a hospitalization, the days hospitalized will not be allocated to both cardiovascular-related and not cardiovascular-related causes.

7.9. Total Blood Volumes

The Laboratory Manual will describe the volume of blood that will be required for each specimen. The only exception is the sample collected for determination of INR and PT, as they will be measured at the site's local laboratory.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious adverse event that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical trial.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Serious adverse events occurring to a subject after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the Sponsor. AEs (both serious and non-serious) should be

recorded on the CRF from the time the subject has taken at least one dose of investigational product through the last subject's last visit.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject, administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose,
- Drug withdrawal,
- Drug misuse,
- Drug interactions,
- Extravasation,
- Exposure during pregnancy (EDP) ,
- Exposure via breastfeeding,
- Medication error,
- Occupational exposure.

8.4. Medication Errors

Medication errors in the study may result from the administration or consumption of the wrong product, by the wrong subject, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error case report form (CRF) which is a specific version of the adverse event (AE) page and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the investigational product,
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is *captured on the medication error version of the adverse event (AE) page* and, if applicable, any associated adverse event(s) are captured on an adverse event (AE) CRF page.

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

1. Test result is associated with accompanying symptoms, and/or
2. Test result requires additional diagnostic testing or medical/surgical intervention, and/or
3. Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
4. Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.6. Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

1. Results in death.
2. Is life-threatening (immediate risk of death).

3. Requires inpatient hospitalization or prolongation of existing hospitalization.

4. Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions).

5. Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject, or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are 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.

The following events must be considered medically important and have the same reporting requirements as SAEs:

- Amyloidosis or heart failure resulting in organ transplantation (regardless if the subject was pre-planned or on a waiting list for an organ prior to study start);

- Amyloidosis or heart failure resulting in cardiac mechanical assist device implantation (regardless if the procedure was pre-planned).

8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections and will be handled as SAEs in the safety database (see the sections on Endpoints and on Serious Adverse Event Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) levels concurrent with abnormal elevations in total bilirubin levels that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual Baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin Baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (X ULN) concurrent with a total bilirubin values ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase values ≤2 X ULN or not available.

- For subjects with preexisting ALT or AST or total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above.

    - For subjects with pre-existing AST or ALT Baseline values above the normal range: AST or ALT values ≥2 times the Baseline values and ≥3 X ULN, or ≥8 X ULN (whichever is smaller).

  Concurrent with:

    - For subjects with pre-existing values of total bilirubin above the normal range: Total bilirubin increased from baseline by an amount of at least 1 X ULN or if the value reaches ≥3 X ULN (whichever is smaller)

The subject should return to the investigational 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 measurement of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in to a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities,
- Hospice facilities,
- Respite care (eg, caregiver relief),
- Skilled nursing facilities,
- Nursing homes,
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment lab abnormality),
- Social admission (eg, subject has no place to sleep),
- Administrative admission (eg, for yearly physical examination,),
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol),
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery),
- Hospitalization for observation without a medical AE,
- Pre-planned treatments or surgical procedures. These should be noted in the Baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

If required on the AE case report forms (CRFs), the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (see Section 8.134.1 on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes, or is found to be pregnant after discontinuing and/or being exposed to the investigational product. An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to the Pfizer Drug Safety Unit on a Serious Adverse Event (AE) report form and Exposure in Utero (EIU) Supplemental Form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EIU Form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EIU reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow-up to the initial EIU Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

1. Spontaneous abortion includes miscarriage and missed abortion.

2. Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the Pregnant Partner Release of Information Form to deliver to his partner. The Investigator must document in the source document that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.11. Occupational Exposure

An occupational exposure occurs when during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an adverse event.

An occupational exposure is reported to drug safety unit within 24 hours of the investigator's awareness, using the SAE Report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a Case Report Form (CRF), however a copy of the completed SAE report form is maintained in the investigator site file.

8.12. Withdrawal Due to Adverse Events (see also Section on Subject Withdrawal and Vital Status / Transplant/Cardiac Mechanical Assist Device Status Follow-up

Withdrawal due to AE should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.13. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

8.14. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy exposure via breastfeeding and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines and/or illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.14.2. Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.14.3. Sponsor's Reporting Requirements to Regulatory Authorities

Adverse event reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1. Sample Size Determination

The primary comparison of interest is the pooled tafamidis 20 mg and 80 mg treatment groups vs. placebo. The target sample size is 400 subjects.

A sample size of 400 subjects is based on findings from study Fx1B-201 (a 12-month, open-label study of tafamidis in TTR-CM subjects), TRACS (an observational study with no treatment intervention other than standard of care in TTR-CM subjects), an understanding of current clinical outcomes in this population, and the uncertainty of the assumptions derived from these limited data.

Given that no closed-form sample size estimation solution is available for the primary analysis method, sample size estimation was performed based on simulations.

Sample size assumptions include:

1. All-cause mortality rate of 12.5% for the tafamidis group and 25.0% for the placebo group (ie, a 50% reduction in mortality with treatment).

2. 1.5 cardiovascular-related hospitalizations for the tafamidis group and 2.5 cardiovascular-related hospitalizations for the placebo group.

3. Treatment duration of 30 months.

4. Significance level (alpha) of 0.05 (two-sided test).

With these assumptions, 300 subjects (n=120 for placebo, n=60 for 20 mg, n=120 for 80 mg) yields a power of over 90% for the primary comparison. A more conservative assumption of 30% reduction in mortality (17.5 % for tafamidis and 25% for placebo) yields a power of approximately 80%. With an assumption of 30% reduction in mortality and increasing the number of subjects to 400 subjects (n=160 for placebo, n=80 for 20 mg, and n=160 for 80 mg) yields a power of approximately 90%.

Summary of operating characteristics:

Assumptions	Sample Size	Power
50% mortality reduction, hosp frequency 2.5 (pbo), 1.5 (taf)	N=300	96%
30% mortality reduction, hosp frequency 2.5 (pbo), 1.5 (taf)	N=300	80%
30% mortality reduction, hosp frequency 2.5 (pbo), 1.5 (taf)	N=400	90%

pbo=placebo, taf=tafamidis

The Sponsor notes that a clinically meaningful change in the all-cause mortality component of the primary analysis could be considered to be as low as a 10% all-cause mortality reduction at 30 months in the comparison between tafamidis and placebo. To power a trial utilizing a primary analysis that assumes this magnitude of treatment effect presents substantial feasibility challenges to study completion due to the relatively small number of subjects identified for potential enrollment in this study.

9.2. Analysis Populations

The intent-to-treat (ITT) analysis set will include all subjects in the safety population who had at least 1 post Baseline efficacy evaluation (ie, post Baseline hospitalization, study visit, or date of death). This may also be referred to as a modified intent-to-treat group but for simplicity will be referred to throughout the protocol and SAP as ITT. The per protocol (PP) analysis set will include all subjects in the ITT set who did not violate inclusion/exclusion criteria and who did not have protocol violations considered to impact the interpretation of the primary efficacy analysis. The safety analysis set will include all subjects who are enrolled (randomized) and received at least 1 dose of double-blind medication.

Both the ITT and PP analysis sets will be used for the primary analysis and for the analyses of the key secondary endpoints, with the ITT being primary. The secondary endpoints and the exploratory endpoints will only be analyzed using the ITT analysis set. The Safety Analysis Set will be used in the analyses of the safety data.

9.2.1. Primary Efficacy Analysis

The primary analysis uses a hierarchical combination of all-cause mortality and frequency of cardiovascular-related hospitalizations (which is defined as the number of times a subject is hospitalized [ie, admitted to a hospital] for cardiovascular-related morbidity) over the duration of the trial. The primary analysis will combine the subjects in the tafamidis 20 mg and tafamidis 80 mg groups (including subjects in the 80 mg group that may have had a dose reduction to 40 mg) into one pooled group. This pooled group (tafamidis) will be compared with the placebo group using the Finkelstein-Schoenfeld method (Finkelstein 1999).[16]

The test is based on the principle that each subject in the clinical study is compared to every other subject within each stratum in a pair-wise manner. The method recognizes the higher importance of all-cause mortality. The pair-wise comparison proceeds in hierarchical fashion using all-cause mortality first, assigning a +1 to the "better" subject and a -1 to the "worse" subject.

- If both subjects are dead, then the subject with a longer survival time is assigned +1.
- If one subject is alive and the other is not, the live subject receives a +1 and the deceased one a -1.
- If both subjects are alive, the comparison uses cardiovascular-related hospitalization to assign scores. The subject with the fewer cardiovascular-related hospitalizations (frequency) receives a +1 while the other receives -1.

The test statistic is based on the sum of these scores and will be stratified by TTR genotype (variant and wild-type) and Baseline severity category (NYHA Classes I and II combined and NYHA Class III).

The null hypothesis for the primary analysis is that neither all-cause mortality nor frequency of cardiovascular-related hospitalizations is different between the tafamidis and placebo treatment groups. The corresponding alternative hypothesis is that at least one and possibly both mortality and frequency of cardiovascular-related hospitalizations are different between the tafamidis and placebo treatment groups.

The term "censored" refers to a subject who discontinues from the trial for reasons other than death. For such subjects, there will be additional follow-up to obtain vital status (and transplant / cardiac mechanical assist device status) at Month 30 and that information will be used in the analysis. In the case where one subject is censored before a second subject has died, and where the vital status of the first subject at Month 30 is missing, then the frequency of cardiovascular-related hospitalizations at the shorter of their follow-up times (the shorter of the 2 subjects' study participation) will be used in assigning a +1 or -1. In the simpler case

where one subject drops out but both are known to be alive at Month 30, the frequency of cardiovascular-related hospitalizations, at the shorter of their follow-up times (the shorter of the 2 subjects study participation), will be used in assigning a +1 or -1. Comparisons of cardiovascular related hospitalization frequency for subjects who completed all 30 months study duration will be based on the earlier of the two actual study durations (days).

Subjects, who discontinue for transplantation (ie, heart transplantation and combined heart and liver transplantation) or for implantation of a cardiac mechanical assist device, will be handled in the primary analysis in the same manner as death. More specifically, the time of the transplant or cardiac mechanical assist device implant will be used in the subject-to-subject comparison in the same manner as if the subject had died at that time (regardless of any additional vital status follow-up information). Data from subjects who drop out for a liver-only transplantation will be handled in the same manner as the data from all other censored subjects.

To examine the potential effect of including heart transplantation or cardiac mechanical assist device as "deaths" in the primary analysis, a sensitivity analysis will be performed treating all transplantation or cardiac mechanical assist device in the same manner as any other censored observation.

As an additional sensitivity analysis, a multiple imputation analysis will be applied using the method developed by Rubin (Rubin 1987). Combined results will be provided for the primary analysis (ie, using Finkelstein-Schoenfeld) as well as for the separate mortality and morbidity elements. Details are provided in the SAP.

9.2.2. Analysis of Key Secondary Endpoints

The key secondary endpoints will be evaluated using a mixed model repeated measures ANCOVA with an unstructured covariance matrix (or as appropriate); center and subject-within-center as random effects; treatment, visit, TTR genotype (variant and wild-type), and visit-by-treatment interaction, as fixed effects and Baseline score as covariate.

The key secondary variables are:

1. Change from Baseline to Month 30 in distance walked during the 6MWT (Appendix 4).

2. Change from Baseline to Month 30 in KCCQ (Appendix 1.1) Overall Summary score.

To maintain the type 1 error rate at or below the specified level, a pre-specified hierarchical order for testing as indicated above will be used to maintain the overall alpha at 0.05 for these two key secondary endpoints. The multiplicity procedure will be applied to the ITT analysis set only.

Supplemental analyses of the two key secondary variables will be performed to support the robustness of the conclusions drawn. The pattern-mixture analysis will group the subjects on the basis of their dropout or missing-data patterns. A grouping variable for this analysis is defined in the SAP.

Exploratory analyses of the key secondary endpoints will include results from the MMRM analysis at each individual time point other than Month 30.

Additional exploratory analyses of the key secondary endpoints will include results from the MMRM analysis at each individual time point by dose group (randomized dose group), TTR genotype (variant and wild-type), and NYHA Baseline classification. Descriptive statistics overall, by dose, by TTR genotype, and by NYHA Baseline classification will be provided for each time point.

Except for the analyses by dose, all analyses of the key secondary endpoints, including the proposed exploratory analyses of these endpoints, will compare the pooled tafamidis group with the placebo group.

9.3. Analysis of Secondary Endpoints

As a secondary analysis, the components of the primary endpoint (ie, all-cause mortality and frequency of cardiovascular-related hospitalizations) will be analyzed separately. All-cause mortality will be analyzed using SAS Proc Lifetest; p-values will be from the log-rank test. Kaplan-Meier survival curves for each treatment group along with median survival times (if applicable) will be presented.

All-cause mortality will also be analyzed using Cox proportional hazards model with treatment, TTR genotype (variant and wild-type), and NYHA Baseline classification (NYHA Classes I and II combined and NYHA Class III) as factors. Frequency of cardiovascular-related hospitalizations will be analyzed using a Poisson regression analysis with treatment, TTR genotype (variant and wild-type), NYHA Baseline classification (NYHA Classes I and II combined and NYHA Class III), treatment-by-TTR genotype interaction, and treatment-by- NYHA Baseline classification interaction terms as factors adjusted for treatment duration.

Cardiovascular-related mortality will also be analyzed using the Kaplan-Meier and Cox proportional methods described above.

All the analyses on the secondary endpoints described above will additionally be presented by TTR genotype (variant versus wild-type), NYHA Baseline classification, as well as dose (randomized dose group), and will be considered exploratory.

The proportion of subjects who achieved TTR stabilization in each treatment group at Month 1 will be compared using a Cochran-Mantel-Haenszel (CMH) test for proportions stratified by TTR genotype and Baseline severity (NYHA Classes I and II combined and NYHA Class III). The analysis will be performed separately by TTR genotypes (variant and wild-type) using a CMH test for proportions stratified by Baseline severity (NYHA Classes I and II

combined and NYHA Class III). The analysis will also be performed separately by Baseline severity (NYHA Classes I and II combined and NYHA Class III) using a CMH test for proportions stratified by TTR genotypes (variant and wild-type).

Analyses of TTR stabilization at Month 1 by dose (low vs. placebo and high vs. placebo) will be compared using a Cochran-Mantel-Haenszel (CMH) test for proportions stratified by TTR genotype and Baseline severity (NYHA Classes I and II combined and NYHA Class III).

A similar test of proportion will be done on TTR stabilization at all other time points and considered exploratory. No subgroup analyses will be done at these other time points.

Except for the analyses by dose group, all analyses of the secondary endpoints, including the proposed exploratory analyses of these endpoints, will compare the pooled tafamidis group with the placebo group.

9.4. Analysis of Exploratory Endpoints

The primary analysis will be repeated by the dose group to which subjects were randomized (tafamidis 20 mg vs. placebo and tafamidis 80 mg vs. placebo) to explore the effect by dose group.

Subgroup analysis using the Finkelstein-Schoenfeld method comparing the pooled tafamidis group and the placebo group, similar to that of the primary analysis, will also be done by the TTR genotype (variant type and the wild-type) and Baseline severity (NYHA Classes I and II combined and NYHA Class III) status.

Frequency of all-cause hospitalization will be analyzed using a Poisson regression analysis with treatment, TTR genotype (variant and wild-type), NYHA Baseline classification, treatment-by-TTR genotype interaction, and treatment-by-NYHA Baseline classification interaction terms as factors adjusted for treatment duration.

Cardiovascular-related days hospitalized and all-cause days hospitalized will be analyzed using an analysis of variance (ANOVA) with treatment, TTR genotype (variant and wild-type), NYHA Baseline classification (NYHA Classes I and II combined and NYHA Class III), treatment-by-TTR genotype interaction, and treatment-by- NYHA Baseline classification interaction terms as factors.

An exploratory analysis based on the Finkelstein-Schoenfeld method similar to that of the primary analysis will be done for each of the combinations of variables listed below:

1. All-cause mortality and frequency of all-cause hospitalization.

2. All-cause mortality and cardiovascular-related days hospitalized.

3. Cardiovascular-related mortality and frequency of cardiovascular-related hospitalization.

The exploratory endpoints listed below will be evaluated at each time point post-Baseline using a MMRM with an unstructured covariance matrix (or as appropriate) with center and subject-within-center as random effects and treatment, visit, TTR genotype (variant and wild-type), and visit-by-treatment interaction, as fixed effects and Baseline score as covariate where applicable (for example, no Baseline will be used as a covariate for PGA):

1. Change from Baseline in Kansas City Cardiomyopathy Questionnaire: (KCCQ) (Appendix 1.1) domain scores (Physical limitation, Symptom stability, Symptom frequency, Symptom burden, Self-efficacy, Social limitation, and Quality of life) and domain summary scores (Functional summary and Clinical summary).

2. Change from Baseline in EuroQoL-5 Dimensions (EQ-5D-3L) (Appendix 2) Index Score and visual analog scale (VAS) scores.

3. Patient Global Assessment (Appendix 3).

4. Change from Baseline in modified Body Mass Index.

5. Change from Baseline in NT-proBNP concentration.

6. TTR concentration and oligomer concentration.

7. Change from Baseline in select echocardiographic parameters:

    a. End-diastolic interventricular septal wall thickness (mm);

    b. Left ventricle posterior wall thickness (mm);

    c. Left ventricular ejection fraction (%);

    d. Left ventricular stroke volume (mL).

    e. Global longitudinal strain;

    f. Circumferential strain mid global;

    g. Radial strain mid global.

All other echocardiographic parameters listed in Section 7.6.5 will be analyzed descriptively.

An increase or decrease in NYHA classification relative to Baseline will be summarized using a shift table at each time point post-Baseline.

9.4.1. Pharmacokinetic Data

Plasma concentrations of tafamidis will be summarized graphically and with descriptive statistics (n, arithmetic mean, standard deviation, coefficient of variation, geometric mean, median, and minimum and maximum) by visit and nominal time. Due to the sparse nature of the pharmacokinetic sampling scheme, a population approach will be used for pharmacokinetic data analysis. Nonlinear mixed-effect modeling will be performed to characterize the pharmacokinetics of tafamidis. These tafamidis concentration data may be pooled with data from previous clinical studies for analysis. Results from any tafamidis concentration modeling conducted will be reportedly separately. If appropriate, these pharmacokinetic data may be used for exposure-response analyses.

To confirm adequate exposures following administration of soft gel capsules in the 80 mg dose group, the Month 1 PK samples from the first 50 subjects enrolled in the study will be analyzed and summarized by treatment to evaluate approximately 20 subjects assigned to the 80 mg dose. The PK sample collection time at the Month 1 visit targets the time of maximum tafamidis concentration at approximately 3 hours post-dose. The expected mean steady state tafamidis concentration is 8.0 ug/mL. If the geometric mean concentration from the 80 mg dose group is < 50% of the projected value, the 80 mg dose may be adjusted. The PK analyst reviewing de-identified tafamidis exposure data will be separate from study team members and will not have access to any unblinded safety or efficacy data. Details of the analysis procedure will be documented in a PK unblinding plan.

9.4.2. Pharmacokinetic/Pharmacodynamic (PK/PD) Modeling

Pharmacokinetic/Pharmacodynamic (PK/PD) modeling of tafamidis treatment groups may be done using the primary and/or secondary efficacy endpoints compared to the corresponding endpoints in the placebo arm. The basic PK/PD model will consist of structural variables for treatment arm and the time points out to 30 months. Additional important covariates (such as demographics) may be added to the PK/PD model during the model building process. The PK/PD model may contain a time course component that will help describe the onset of action as compared to the placebo arm. Other efficacy, safety, and exploratory endpoints may also be modeled as needed to further understand tafamidis response variables. Results from any tafamidis PK/PD modeling conducted will be reportedly separately.

9.5. Safety Analysis

The safety assessments in the study are listed in Section 7.6. All randomized subjects who receive at least one dose of study treatment will be included in the safety analysis. All adverse events that are observed from the time of first dosing with study medication (at randomization) until the end of study participation will be included in the safety analysis. Adverse events that occurred during treatment will be reported separately if the event occurred prior to randomization.

All adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by treatment group. The incidence of treatment-emergent adverse events will be tabulated by treatment group and by system organ class. The incidence of treatment-emergent adverse events will be displayed by severity and

attribution. In addition, the incidence of serious adverse events and adverse events that cause withdrawal will be tabulated. All adverse events will be listed.

The following 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers. Different analyses will be performed for different tiers and will be documented in the statistical analysis plan.

> Tier-1 events: These are pre-specified events of clinical importance and are maintained in a list in the product's Safety Review Plan. This list may be updated as more is understood about the drug.
>
> Tier-2 events: These are events that are not Tier-1 but are "common". A MedDRA Preferred Term (PT) is defined as a Tier-2 event if there are at least 4 in any treatment group.
>
> Tier-3 events: These are events that are neither Tier-1 nor Tier-2 events.

All clinical laboratory data will be subjected to clinical review and summarized by frequency of events and mean changes from Baseline.

All vital sign measurements will be displayed in listings by subject for each sample collection date and time. The measurement taken immediately prior to randomization will be used as the Baseline value for calculating changes in vital signs.

Centrally over-read ECG variables will be summarized by mean change from Baseline to each measurement time for heart rate, PR interval, QRS width, QT interval, and QTcB (Bazett's correction) and QTcF (Fridericia's correction) values. Additionally, the incidence of categorical increases in QTc intervals will be provided. Categories for QTcB and QTcF are $\geq$ 450 msec, $\geq$480 msec, and $\geq$ 500 msec. Categories for QTcB and QTcF as change from Baseline are: $\geq$ 30 msec increase, $\geq$ 60 msec increase, and $\geq$ 75 msec increase. QTcF is considered the primary QTc value as this correction is anticipated to be more appropriate.

All of the analysis on the safety endpoints will compare placebo with each tafamidis dose (20 mg and 80 mg) as well as the pooled group (combined tafamidis 20 mg and 80 mg).

The safety analyses will also be summarized by TTR genotype and NYHA Baseline classification.

9.6. Data Monitoring Committee

This study will use an External Data Monitoring Committee (E-DMC) that is independent from Pfizer. Information regarding the E-DMC can be found in the External Data Monitoring Committee Charter, including the membership of the committee.

The E-DMC will be responsible for ongoing monitoring of the safety of subjects in the study according to the E-DMC Charter through safety interim analyses of comparisons of safety information across treatment groups. Any recommendations made by the E-DMC to alter the

conduct of the study based on safety findings will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data which are not endpoints, to regulatory authorities, as appropriate.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the Institutional Review Board (IRB)/ Ethics Committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer 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 subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

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.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, (eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, (eg, recruitment advertisements, if applicable, from the IRB/IEC). All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 & 2008).[24,12]

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or in other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study subjects. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

The informed consent documents and any subject recruitment materials must be in compliance with ICH, GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject (or a legal representative), is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

12.4. 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 Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, 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 subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH/GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient subjects have been recruited and completed the study as stated in the regulatory application (ie, Clinical Trial Application (CTA) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in all other Participating Countries

End of Trial in all other participating countries is defined as Last Subject Last Visit.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of tafamidis at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 30 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of this study on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT) and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

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 US Basic Results on www.clinicaltrials.gov for all Pfizer-sponsored interventional studies that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations

Primary completion date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

EudraCT

Pfizer posts clinical trial results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

15.2. Publications by Investigators

Pfizer has no objection to publication by Investigator of any information collected or generated by Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

Investigator will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

If the Study is part of a multi-center study, Investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the Study at all participating sites, Investigator is free to publish separately, subject to the other requirements of this Section.

For all publications relating to the Study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

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Appendix 1. Patient Reported Outcomes

Appendix 1.1. KCCQ

THE KANSAS CITY CARDIOMYOPATHY QUESTIONNAIRE: (KCCQ)

The following questions refer to your heart failure and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. Heart Failure affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by heart failure (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Place an X in one box on each line

Activity	Extremely limited	Quite a bit limited	Moderately limited	Slightly limited	Not at all limited	Limited for other reasons or did not do the activity
Dressing yourself						
Showering/Bathing						
Walking 1 block on level ground						
Doing yardwork, housework or carrying groceries						
Climbing a flight of stairs without stopping						
Hurrying or jogging (as if to catch a bus)						

2. Compared with 2 weeks ago, have your symptoms of heart failure (shortness of breath, fatigue or ankle swelling) changed? My symptoms of heart failure have become…

Much worse	Slightly worse	Not changed	Slightly better	Much better	I've had no symptoms over the last 2 weeks

3. Over the past 2 weeks, how many times did you have swelling in your feet, ankles or legs when you woke up in the morning?

Every	3 or more times	1-2 times a	Less than once	Never over the

morning	a week, but not every day	week	a week	past 2 weeks

4. Over the past 2 weeks, how much has swelling in your feet, ankles or legs bothered you?

In has been…

Extremely bothersome	Quite a bit bothersome	Moderately bothersome	Slightly bothersome	Not at all bothersome	I've had no swelling

5. Over the past 2 weeks, on average, how many times has fatigue limited your ability to do what you want?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks

6. Over the past 2 weeks, how much has your fatigue bothered you?

It has been…

Extremely bothersome	Quite a bit bothersome	Moderately bothersome	Slightly bothersome	Not at all bothersome	I've had no fatigue

7. Over the past 2 weeks, on average, how many times has shortness of breath limited your ability to do what you wanted?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	2 times per week	Less than once a week	Never over the past 2 weeks

8. Over the past 2 weeks, how much has your shortness of breath bothered you?

Extremely bothersome	Quite a bit bothersome	Moderately bothersome	Slightly bothersome	Not at all bothersome	I've had no shortness of breath

9. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of shortness of breath?

Every night	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks

10. Heart Failure symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if your heart failure gets worse?

Not at all sure	Not very sure	Somewhat sure	Mostly sure	Completely sure

11. How well do you understand what things you are able to do to keep your heart failure symptoms from getting worse? (for example, weighing yourself, eating a low salt diet, etc.)

Do not understand at all	Do not understand very well	Somewhat understand	Mostly understand	Completely understand

12. Over the past 2 weeks, how much has your heart failure limited your enjoyment of life?

It has extremely limited my enjoyment of life	It has limited my enjoyment of life quite a bit	It has moderately limited my enjoyment of life	It has slightly limited my enjoyment of life	It has not limited my enjoyment of life at all

13. If you had to spend the rest of your life with your heart failure the way it is right now, how would you feel about this?

Not at all satisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied

14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your heart failure?

I felt that way all of the time	I felt that way most of the time	I occasionally felt that way	I rarely felt that way	I never felt that way

15. How much does your heart failure affect your lifestyle? Please indicate how your heart failure may have limited your participation in the following activities over the past 2 weeks?

Please place an X in one box on each line

Activity	Severely limited	Limited quite a bit	Moderately limited	Slightly limited	Did not limit at all	Does not apply or did not do for other reasons
Hobbies, recreational activities						
Working or doing household chores						
Visiting family or friends out of your home						
Intimate relationships with loved ones						

Developed by John Spertus et al., Mid America Heart Institute, Saint Luke's Hospital, Kansas City, MO.

Appendix 2. EQ-5D-3L

DATA CLASS: EUROQOL 5 DIMENSIONAL HEALTH STATE QUESTIONNAIRE (E5D) VERSION 1.4.0

E5D001

EQ-5D HEALTH QUESTIONNAIRE - SUBJECT VERSION: (Page 2 of 2)

By placing a check mark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility
- I have no problems in walking about ☐
- I have some problems in walking about ☐
- I am confined to bed ☐

Self-Care
- I have no problems with self-care ☐
- I have some problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

Usual Activities (e.g. work, study, housework, family or leisure activities)
- I have no problems with performing my usual activities ☐
- I have some problems with performing my usual activities ☐
- I am unable to perform my usual activities ☐

Pain/Discomfort
- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐

Anxiety/Depression
- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extremely anxious or depressed ☐

VARIABLE INFORMATION: <1> = Pre-print exam, collection, test, etc. as per protocol.
<3> = Choices for language administered are in codelist 'LANGUA'.

OPTIONAL INFORMATION: <2> = This item is optional.

DESIGN GUIDELINE:
The following should be added to all DCT translation documents: Copyright of all language versions of EQ-5D is held by the EuroQol Group

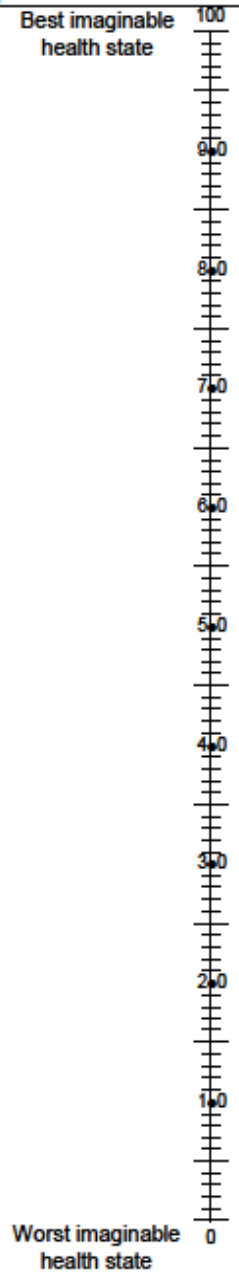
DATA CLASS: EUROQOL 5 DIMENSIONAL HEALTH STATE QUESTIONNAIRE (E5D) VERSION 1.4.0

EQ-5D HEALTH QUESTIONNAIRE - SUBJECT VERSION: ESD001a

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Investigator Use Only

Score ⌊_⌋

Appendix 3. PGA

PGA Item for Baseline Visit:

Taking your cardiomyopathy into account, would you say the state of your health is:

- Normal, not at all ill;
- Borderline ill;
- Mildly ill;
- Moderately ill;
- Markedly ill;
- Severely ill;
- Among the most extremely ill.

PGA Item for Follow-Up Visits:

Place an X in the box you feel most closely describes any change which you have experienced since beginning the study medication.

Take into account all change, whether or not you believe it is entirely due to drug treatment.

Choose only ONE response.

Since starting the study medication, my cardiomyopathy (HEART FAILURE) is:

☐ Very Much Improved

☐ Much Improved

☐ Minimally Improved

☐ No Change

☐ Minimally Worse

☐ Much Worse

☐ Very Much Worse

Appendix 4. 6-Minute Walk Test

The walking test should be performed indoors, along a long, flat, straight enclosed corridor with a hard surface that is seldom traveled. The walking course should be 30 meters in length. A 100 foot hallway is, therefore, required. The length of the hallway should be marked every 3 meters. The starting line should be clearly marked with bright colored tape. A treadmill is NOT recommended.

Study Coordinator/Observers: Should be trained using the standard protocol and then supervised before performing the test alone. They should have completed cardiopulmonary resuscitation training.

Required Equipment:

1. Countdown timer/Stopwatch.
2. Mechanical lap counter.
3. Two small cones to mark the turnaround points.
4. A chair that can be easily moved along the walking course.
5. Worksheets on a clipboard.
6. A source of oxygen.
7. Sphygmomanometer.
8. Telephone.
9. Automated electronic defibrillator.

Subject Preparation:

1. Comfortable clothing should be worn.
2. Appropriate shoes for walking should be worn.
3. Subjects should use their usual walking aids for the test (cane, walker, etc).
4. The subject's usual medical regimen should be continued.
5. A light meal is acceptable before early morning or early afternoon tests.
6. Subject should not have exercised vigorously within 2 hours of beginning the test.

Measurements:

1. Where possible, repeat testing should be performed about the same time of day to minimize variability.

2. A "warm-up" period before the test should NOT be performed.

3. The subject should sit at rest for about 10 minutes before the test starts. Complete the first part of the work sheet.

4. Pulse oximetry is optional.

5. Have the subject stand and rate their Baseline dyspnea and overall fatigue using the Borg scale.

The Borg Scale:

0 – Nothing at all

0.5 – Very, very slight (just noticeable)

1 – Very slight

2 – Slight (light)

3 – Moderate

4 – Somewhat severe

5 – Severe

6

7 – Very severe

8

9

10 – Very, very severe (maximal)

Ask the subject what their level of shortness of breath is and then ask what their level of fatigue is.

1. Set the lap counter to zero and the timer to 6 minutes. Assemble all necessary equipment, and move to starting point.

2. Instructions to the subject:

a. "The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as possible as you are able;

b. You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. "Now I'm going to show you. Please watch the way I turn without hesitation";

c. Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly;

d. "Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE in 6 minutes, but don't run or jog;

e. Do you have any questions?

f. Start now or whenever you are ready."

3. Position the subject at the starting line. You should also stand near the starting line during the test. Do not walk with the subject. As soon as the subject starts to walk, start the timer.

4. Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the subject. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, click the lap counter once (or mark the lap on the worksheet). Let the participant see you do it. Exaggerate the click using body language, like using a stop-watch at a race.

a. After the first minute, tell the subject the following (in an even tone) **"You are doing well. You have 5 minutes to go."**

b. When the timer shows 4 minutes remaining, tell the subject the following: **"You have 4 minutes to go."**

c. When the timer shows 3 minutes remaining, tell the subject the following: **"You are doing well. You are half way done."**

d. When the timer shows 2 minutes remaining, tell the subject the following: "Keep up the good work. You have only 2 minutes left."

e. When the timer shows only 1 minute remaining, tell the subject: **"You are doing well. You have only 1 minute to go."**

f. Do not use other words of encouragement (or body language to speed up).

g. If the subject stops walking during the test and needs a rest, say this: **"You can lean against the wall if you would like; then continue walking whenever you feel able."** Do not stop the timer. If the subject stops before the 6 minutes are up and refuses to continue (or decides that they should not continue), wheel the chair over for the subject to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped and the reason for stopping prematurely.

5. Post-test: Record the post walk Borg dyspnea and fatigue levels and ask this: **"What, if anything, kept you from walking farther?"**

6. If using a pulse oximeter, measure SpO2 and pulse rate from the oximeter and then remove the sensor.

7. Record the number of laps from the counter (or tick marks from the worksheet).

8. Record the additional distance covered (the number of meters in the final partial lap) using the markers on the wall as distance guides. Calculate the total distance walked, rounding to the nearest meter, and recording it on the worksheet.

9. Congratulate the subject on a good effort and offer a drink of water.