A PHASE 3 MULTICENTER, OPEN-LABEL STUDY TO EVALUATE THE SAFETY OF DAILY ORAL DOSING OF TAFAMIDIS MEGLUMINE (PF-06291826-83) 20 MG OR 80 MG [OR TAFAMIDIS (PF-06291826-00) 61 MG] IN SUBJECTS DIAGNOSED WITH TRANSTHYRETIN CARDIOMYOPATHY (ATTR-CM)

Compound:	PF-06291826
Compound Name:	Tafamidis
United States (US) Investigational New Drug (IND) Number:	IND 71,880
European Clinical Trials Database (EudraCT) Number:	2016-000868-42
Protocol Number:	B3461045
Phase:	3

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 5 (country specific)	24 January 2020	1. For newly enrolled subjects in countries listed in Appendix 6, addition of blood and urine sample collection for additional banked biomarker sample collection, as described in Appendix 7. 2. For newly enrolled subjects in countries listed in Appendix 6, addition of blood and urine sample collection to support identification and characterization of biomarkers of transthyretin amyloidosis, as described in Appendix 7. 3. For newly enrolled subjects in countries identified in Appendix 6, addition of collection of echocardiography parameters from medical history, as described in Appendix 7.
Amendment 4 (Global)	09 August 2019	1. Update total subject enrollment from 1400 to 2000 and Appendix 5 countries participating in Cohort B. 2. Addition of blood sample collection for testing of cardiac biomarkers N-terminal pro-hormone brain natriuretic peptide (NT-proBNP) and troponin I. 3. Clarification that previously experimental therapies patisiran and inotersen remain study prohibited as commercial therapies. 4. Clarification of adverse event monitoring telephone contact for subjects enrolled in Japan in Appendix 4.2. 5. Minor formatting/grammar/readability improvements in general.
Amendment 3 (Global)	20 July 2018	1. Addition of a second cohort to enroll ATTR-CM diagnosed subjects who did not participate in parent study B3461028.

		2. Transition of all subjects to open label 61 mg dose (where available) as a result of the parent study dose decision confirmation. 3. Transition of IP packaging from blinded blister packs to open label bottle packaging. 4. Required contraception, highly effective contraception methods, and definition of woman of childbearing potential updated to align with new common protocol template language. 5. Add banked biospecimen collection for new cohort. 6. Minor formatting/grammar/readability improvements in general.
Amendment 2 Country Specific (Germany)	28 March 2017	1. Addition of Germany to the France-only country specific procedures at Month 3 visit.
Amendment 1 Country Specific (France and Germany)	31 January 2017	1. (France and Germany) Title Page: Added European Clinical Trials Database (EudraCT) Number. 2. (France and Germany) Protocol Summary, Section 3 Study Design: Specified study will end 24 months after the initial protocol approval date by the local Competent Authority. Continuation after the initial protocol approval period will depend on review of the final Clinical Study Report for parent study B3461028 by the local Competent Authority. 3. (France only) Schedule of Activities: Added the following procedures to Month 3 visit: 1) Physical examination and weight measurement 2) 12-Lead ECG 3) Vital signs measurement 4) Blood/urine sample collection 5) Pregnancy testing 6) Administer Kansas City

		Cardiomyopathy Questionnaire (KCCQ) 7) New York Heart Association (NYHA) classification 8) Drug compliance and accountability. 4. (France only) Section 6.2.2 Telephone visit procedures: Specified additional procedures at Month 3 visit. 5. (France only) Section 7.1.2 Physical Examination and Height Measurements: Specified brief physical examination at Month 3 visit. 6. (France only) Section 7.1.3 Vital Signs: Specified Vital signs measurement at Month 3 visit. 7. (France only) Section 7.1.4 Electrocardiogram: Specified ECG measurement at Month 3 visit. 8. (France only) Section 7.1.5 Clinical Laboratory Tests: Specified blood/urine sample collection for Hematology, Serum Chemistry, Coagulation, Urinalysis at Month 3 visit. 9. (France only) Section 7.2 Pregnancy Testing: Specified pregnancy test to be performed at Month 3. 10. (France only) Section 7.4.1 New York Heart Association Classification: Specified NYHA classification at Month 3 visit. 11. (France only) Section 7.4.2 Kansas City Cardiomyopathy Questionnaire: Specified KCCQ administration at Month 3 visit.
Original protocol	29 January 2016	Not applicable (N/A)

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

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PROTOCOL SUMMARY

Background and Rationale:

Pfizer is developing tafamidis, an oral small molecule, for the treatment of transthyretin amyloid diseases. Transthyretin cardiomyopathy (TTR-CM or ATTR-CM) occurs when transthyretin (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.

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. It is hypothesized that tafamidis would stop or slow the progression of ATTR-CM and therefore represents a disease modifying therapy.

Study B3461028 was a 30-month, Phase 3, double-blind, placebo-controlled, randomized, parallel-group trial designed to evaluate the efficacy, safety and tolerability of oral dosing of tafamidis meglumine 20 mg or 80 mg in comparison to placebo in subjects diagnosed with transthyretin cardiomyopathy and heart failure. Subject population was 441 male and female subjects aged 18 to 90 years, with ATTR-CM due to either variant, or wild type TTR. The study completed with sites in North and South America, the European Union, and Japan. The primary analysis was all-cause mortality and the frequency of cardiovascular-related hospitalizations. The primary analysis demonstrated a statistically significant reduction in the combination of all-cause mortality and frequency of cardiovascular-related hospitalizations compared to placebo. The preliminary safety data showed that tafamidis was generally well tolerated in this population and no new safety signals were identified.

The B3461045 protocol was designed as a long-term extension safety study for subjects completing 30 months of blinded treatment on Study B3461028. Given the positive results of the B3461028 study and the favorable benefit to risk profile there is a justification to provide patients with an option for early access to tafamidis. Consequently, the B3461045 study protocol will be amended herein to include an additional cohort of patients with ATTR-CM who have not previously participated in the B3461028 parent study. The purpose of the additional cohort is to provide these patients early access to tafamidis, until local availability by prescription for the ATTR-CM indication.

Additionally, a new formulation which is bioequivalent to tafamidis meglumine 80 mg has been developed and is presented as tafamidis 61 mg (as the free acid). This formulation, where available, will replace the tafamidis meglumine 80 mg dose after protocol amendment 3.

Objectives and Endpoints:

Primary Objectives:

- To obtain additional, long-term, safety data for tafamidis in subjects with transthyretin amyloid cardiomyopathy (ATTR-CM).
- To provide investigational product, tafamidis, to enrolled subjects until local availability by prescription for the ATTR-CM indication.

Primary Endpoints:

Safety as measured by:

- All-cause mortality.
- Incidence of treatment-emergent adverse events.

Other Endpoints:

- Cardiovascular-related mortality.
- Frequency of all-cause hospitalization.
- Frequency of cardiovascular-related hospitalization (including heart failure, arrhythmia, myocardial infarction, stroke and other cardiovascular-related events).
- Change from baseline at each visit in Kansas City Cardiomyopathy Questionnaire Overall Summary score, domain scores (Physical limitation, Symptom stability, Symptom frequency, Symptom burden, Total symptom, Self-efficacy, Social limitation, and Quality of life), and Clinical summary score.
- New York Heart Association (NYHA) classification at each visit.
- Change from baseline in Body Mass Index/modified Body Mass Index (BMI/mBMI) at each visit.
- Change from baseline in N-terminal pro-hormone brain natriuretic peptide (NT-proBNP) concentration at each visit.
- Change from baseline in Troponin I concentration at each visit.
- Assessment of physical examinations, use of concomitant medications, electrocardiograms (ECGs), clinical laboratory testing, vital signs at each visit.

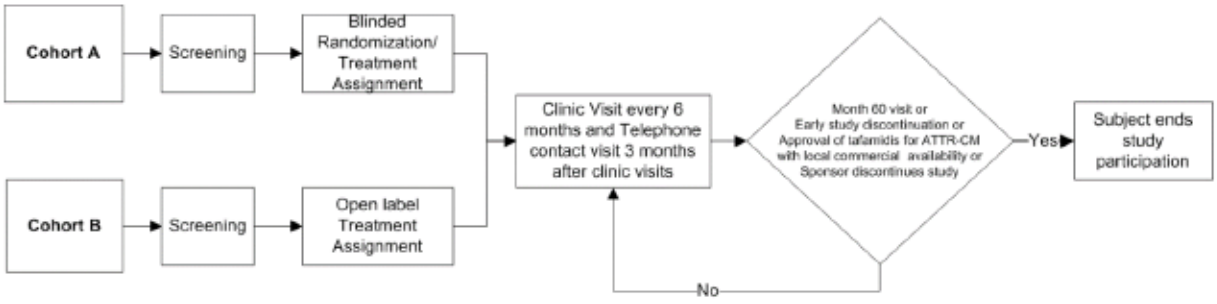
Study Design:

This is a Phase 3, open-label long-term extension safety study designed to obtain additional safety data for tafamidis meglumine 20 mg and 80 mg (or tafamidis 61 mg where available), and to continue to provide enrolled subjects with tafamidis for up to 60 months, or until subject has access to tafamidis for ATTR-CM via prescription, whichever occurs first. The study will also end before 60 months if the sponsor discontinues the study. Subjects withdrawn from the study due to commercial access to prescription tafamidis in their respective countries will be considered study completers. The decision to withdraw subjects for transition to commercial tafamidis will be made by the sponsor.

Eligible study participants will be enrolled in 2 cohorts:

- Cohort A – Subjects diagnosed with ATTR-CM who completed 30 months of participation in Study B3461028.
- Cohort B – Subjects diagnosed with ATTR-CM who have not previously participated in Study B3461028 (Appendix 5).

Study Participation Flow



Subjects in Cohort A will be assigned to open label treatment after protocol amendment 3.

Duration of Study Participation

Study duration is for up to 60 months or until local commercial availability of tafamidis by prescription for ATTR-CM indication is achieved, whichever occurs first. The study will also end before 60 months if the sponsor discontinues the study.

Selection of Subjects:

Cohort A Inclusion Criteria:

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

1. Male and female subjects with TTR amyloid cardiomyopathy who have completed 30 months of study treatment on Protocol B3461028.

2. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.

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

4. Male subjects able to father children and female subjects of childbearing potential and at risk for pregnancy must agree to use 2 highly effective methods of contraception throughout the study and for at least 28 days after the last dose of assigned treatment.

   Female subjects who are not of childbearing potential (ie, meet at least 1 of the following criteria):

   - Have undergone a documented hysterectomy and/or bilateral oophorectomy;
   - Have medically confirmed ovarian failure; or
   - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by having a serum follicle- stimulating hormone (FSH) level confirming the post-menopausal state.

   All other female subjects (including females with tubal ligations) will be considered to be of childbearing potential.

Cohort B Inclusion Criteria:

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

1. Male or female subject of at least 18 years of age (or the minimum country specific age of consent if >18) and participates at a study site in an eligible country listed in Protocol Appendix 5.

2. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.

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

4. A female subject is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

   - Is not a Woman of Childbearing Potential (WOCBP) (see definition Section 4.3.1).

   OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year) (see Section 4.3) during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any study intervention. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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

5. Documentation of the genetic testing for transthyretin amyloidosis (ie, original laboratory result, or copy).

6. Documentation of diagnosis and criteria used (eg, congestive heart failure and scintigraphy with tracer eg, *99mTC DPD [99mTC 3,3 diphosphono 1,2 propano dicarboxylic acid], 99mTC PYP [Pyrophosphate] and also 99mTC HMDP [hydroxymethylene diphosphonate]* or congestive heart failure and presence of amyloid deposits in biopsy tissue, *eg, fat aspirate, salivary gland, median nerve connective tissue sheath, or cardiac [amyloid demonstrated per appropriate stain such as Congo red or alcian blue stain*]).

7. Documentation that primary (light chain) amyloidosis disease has been evaluated and ruled out (ie, original laboratory result, or copy).

8. Evidence of NYHA classification I, II, III, or IV.

Cohort A Exclusion Criteria:

Subjects in Cohort A with any of the following characteristics/conditions will not be included in the study:

1. Chronic use of diflunisal, TTR stabilizer, tauroursodeoxycholate, doxycycline, digitalis, patisiran, calcium channel blockers, investigational drug(s) or other experimental interventions, other than tafamidis, independently or as part of a study within 30 days prior to enrollment or inotersen within 6 months prior to enrollment.

2. Use of certain non-steroidal anti-inflammatory drugs (NSAIDs) [Section 5.8.1].

3. Liver and/or heart transplant, or implanted cardiac mechanical assist device.

4. Pregnant female subjects (or planning to become pregnant during the study interval); breastfeeding female subjects; male subjects with partners currently pregnant.

5. Require initiation of treatment with calcium channel blockers.

6. Urinary retention requiring chronic self-catheterization.

7. Breach of compliance with treatment/significant protocol violations during conduct of B3461028 for which the subject was accountable.

8. Subjects who are investigational site staff members directly involved in the conduct of the study 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 study.

9. 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 that 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.

Cohort B Exclusion Criteria:

Subjects in Cohort B with any of the following characteristics/conditions will not be included in the study:

1. Chronic use of diflunisal, TTR stabilizer, tauroursodeoxycholate, doxycycline, digitalis, patisiran, calcium channel blockers, investigational drug(s) or other experimental interventions, other than tafamidis, independently or as part of a study within 30 days prior to enrollment or inotersen within 6 months prior to enrollment.

2. Use of certain non-steroidal anti-inflammatory drugs (NSAIDs) [Section 5.8.1].

3. Liver and/or heart transplant, or implanted cardiac mechanical assist device.

4. Require initiation of treatment with calcium channel blockers.

5. Urinary retention requiring chronic self-catheterization.

6. 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.

7. Subjects who are investigational site staff members directly involved in the conduct of the study 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 study.

8. 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 that 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.

Study Treatments:

Subject eligibility for participation in the treatment phase of the protocol will be determined following the assessments at the Screening 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 enrolled. There will be treatment assignment stratification by TTR genotype (variant or wild-type) for Cohort A.

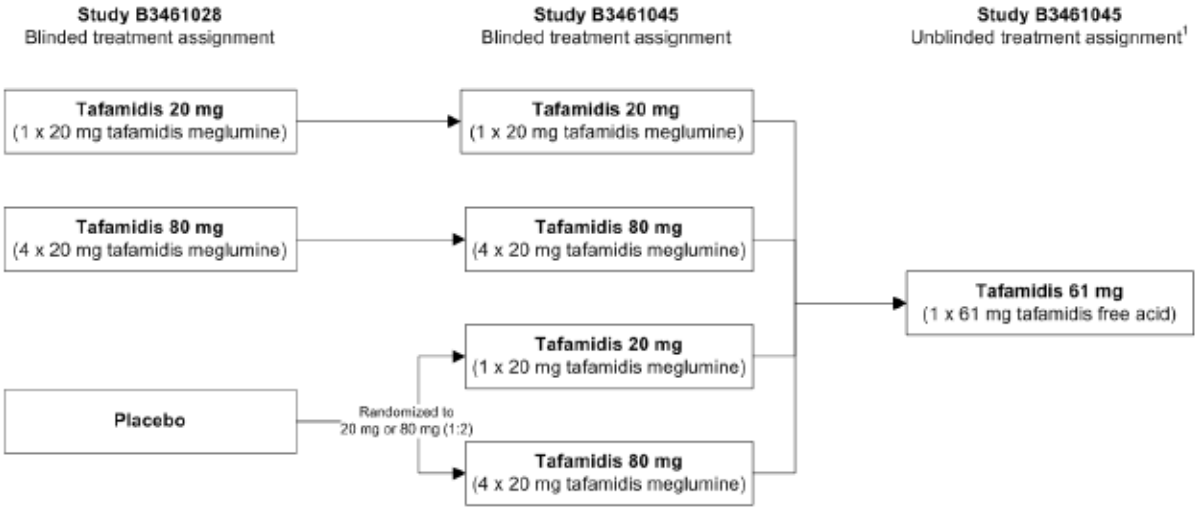
Cohort A Treatment Assignments:

At enrollment, subjects in Cohort A were assigned to blinded active treatment; 20 mg or 80 mg tafamidis once daily, in addition to standard of care (eg, diuretics) for up to 60 months based on the following:

- Subjects receiving 20 mg or 80 mg tafamidis in Study B3461028 continue the same blinded treatment assignment.
- Subjects assigned to placebo in Study B3461028 will be randomized (1:2) to blinded 20 mg or 80 mg tafamidis. Subjects assigned to placebo in Study B3461028 and randomized to 80 mg tafamidis will be permitted one blinded dose-reduction to 20 mg for adverse events related to tolerability.

Subjects in Cohort A will be assigned to open label treatment after protocol amendment 3.

Subjects receiving 20 mg or 80 mg tafamidis meglumine will be assigned to 61 mg tafamidis, once daily, in addition to standard of care (eg, diuretics), for up to 60 months. Subjects will be assigned to 80 mg tafamidis meglumine in regions where 61 mg tafamidis is unavailable.



[1]One permanent dose reduction to 20 mg tafamidis meglumine is permitted for adverse events related to tolerability; Subjects will be assigned to 80 mg tafamidis meglumine in regions where 61 mg tafamidis is unavailable

Cohort B Treatment assignment:

At enrollment, subjects in Cohort B will be assigned to open label 61 mg tafamidis once daily, in addition to standard of care (eg, diuretics), for up to 60 months. One dose reduction to 20 mg tafamidis meglumine will be permitted for adverse events related to tolerability. Subjects will be assigned to 80 mg tafamidis meglumine in regions where 61 mg tafamidis is unavailable.

Investigational Product Supplies

Tafamidis meglumine is available in 20 mg soft gel capsules. Tafamidis free acid is available in 61 mg soft gel capsules.

Dosage Level (Compound)	Appearance	Number of Capsules Per Day (Dose)
Tafamidis meglumine 20 mg (PF-06291826-83) - blinded	Yellow, oblong soft gelatin capsules	1 (Tafamidis meglumine 20 mg capsule) 3 (Placebo capsules)
Tafamidis meglumine 80 mg (PF-06291826-83) - blinded	Yellow, oblong soft gelatin capsules	4 (Tafamidis meglumine 20 mg capsules)
Tafamidis free acid 61 mg (PF 06291826-00) - open	Reddish brown, oblong soft gelatin capsules	1 (Tafamidis free acid 61 mg capsule)
Tafamidis meglumine 20 mg (PF 06291826-83) - open	Yellow, oblong soft gelatin capsules	1 (Tafamidis meglumine 20 mg capsule)
Tafamidis meglumine 80 mg (PF 06291826-83) - open	Yellow, oblong soft gelatin capsules	4 (Tafamidis meglumine 20 mg 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 Rationale

There is no formal sample size calculation for this protocol. Subjects who meet enrollment criteria are eligible; Up to 2000 subjects are expected to enroll in Study B3461045.

Analysis Populations

The safety analysis population consists of all subjects who are enrolled in this study and who have taken at least one dose of study treatment. For specific mortality-related analysis, treated subjects from the parent study B3461028 who discontinue prior to the start of this study will also be included.

Statistical Objective

This study is primarily descriptive in nature. Hypothesis testing will be applied to a limited set of variables.

Planned Interim Analysis

Interim analyses will be performed if required to meet regulatory requirements (eg, annual reporting) and as requested by the External Data Monitoring Committee. Interim analyses may also be performed during the course of the study to allow for the reporting of data to the scientific community.

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the 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, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Visit Identifier	Screening			Day 1	*Month 3*	Telephone Visits[b]	Clinic Visits[c]	End of Study Visit[d]	Post-study follow-up[e]
Population	Cohort B[a] (without disease documentation)		Cohort A[a] & Cohort B[a,u] (with disease documentation)	Cohorts A & B	*(Appendix 4.2 country requirement)*[b]	Cohorts A & B			
Frequency					*Month 3*	Every 6 months	Every 6 months	Month 60 or Early Study Termination	28 days after last dose
Visit Window[f]	Day -30	Day 0	Day 0	Day 1	*±2 weeks*	±2 weeks	±2 weeks	±2 weeks	
Informed consent and Release of Medical Information Form	X		X						
Inclusion/exclusion criteria	X	X	X						
Demography	X		X						
Medical history	X		X						
Physical examination (full)[g]		X	X					X	
Physical examination (brief)[h]			X[g]		*X*		X		
Height measurement[i]		X	X						
Vital Signs[j]		X	X		*X*		X	X	
Laboratory Testing[k,l]									
Hematology		X	X[l]		*X*		X	X	
Serum Chemistry		X	X[l]		*X*		X	X	
Coagulation		X	X[l]		*X*		X	X	
Retinol Binding Protein		X	X[l]		*X*		X	X	
Urinalysis		X	X		*X*		X	X	
Cardiac biomarkers (NT-proBNP, troponin I)[x]		X	X		*X*		X	X	
Serum/urine test for primary (light chain) amyloidosis	X								
Genotyping	X								
Tissue Biopsy	X								
Banked biospecimens[w]		X[w]	X[w]						
Additional Country-specific Sample and Banked Biospecimen Collection[y]		X	X						
Pregnancy test for women of childbearing potential[k]		X	X		*X*		X	X	
Contraception check[m]		X	X		*X*	X	X	X	X
Enrollment/randomization[v]		X	X						
Dispense tafamidis[n]		X	X		*X*	X	X		
First dose of tafamidis				X[o]					
Clinical Assessments									
NYHA Classification		X	X		*X*		X	X	
KCCQ		X	X		*X*		X	X	
12-lead ECG[p]		X	X		*X*		Annual[p]	X[q]	
Hospitalization determination[r]					*X*	X	X	X	
IP compliance/accountability					*X*	X	X	X	
Documentation of Vital, Transplant, CMAD Status[s,t]	X	X	X		*X*	X	X	X[t]	

Visit Identifier	Screening			Day 1	*Month 3*	Telephone Visits[b]	Clinic Visits[c]	End of Study Visit[d]	Post-study follow-up[e]
Population	Cohort B[g] (without disease documentation)		Cohort A[a] & Cohort B[a,g] (with disease documentation)	Cohorts A & B	*(Appendix 4.2 country requirement)[b]*	Cohorts A & B			
Frequency					*Month 3*	Every 6 months	Every 6 months	Month 60 or Early Study Termination	28 days after last dose
Visit Window[f]	Day -30	Day 0	Day 0	Day 1	*±2 weeks*	±2 weeks	±2 weeks	±2 weeks	
Concomitant Treatments	X	X	X	→	→	→	→	X	
Adverse Event Reporting	X	X	X	→	→	→	→	→	X[e]

Abbreviations: → = ongoing/continuous event; ECG = electrocardiogram; KCCQ = Kansas City Cardiomyopathy Questionnaire; NYHA = New York Heart Association.

a. **Cohort A**: Screening Visit/Day 0 is the End of Study visit and last day of treatment for Study B3461028. Study procedures and assessments will be performed once per subject and the protocol-specified data reported separately for each study. Subjects providing consent and fulfilling the inclusion/exclusion criteria will be enrolled, randomized, and dispensed study medication for Study B3461045 at the same visit. Subjects will be instructed to start self-administration of tafamidis the following day (Day 1). If more than 30 days have elapsed from the B3461028 End of Study visit, then vital signs, a brief physical examination, clinical laboratory tests, contraception check, concomitant medications, adverse event reporting must be performed on Day 0 prior to enrollment. Subjects in Cohort A will be assigned to open label treatment after protocol amendment 3.

   Cohort B: Subjects who have the following available at screening (documentation of the genetic testing for transthyretin amyloidosis, documentation of diagnosis and criteria used and documentation that primary light chain amyloidosis disease has been evaluated and ruled out) may have all screening procedures performed on Day 0. In addition to providing consent and fulfilling the inclusion/exclusion criteria will be enrolled and dispensed study medication for Study B3461045 at the same visit.

b. Telephone visits will be performed on Months 3, 9, 15, 21, 27, 33, 39, 45, 51, and 57. Telephone visit procedures may also be performed at the study site. *For countries listed in Appendix 4.2 only: Subjects are required to return to the study site for additional procedures at Month 3.*

c. Clinic visits will be performed at Months 6, 12, 18, 24, 30, 36, 42, 48, and 54.

d. End of Study visit will occur upon subject completion of study at Month 60, subject withdrawal (for any reason), or study discontinuation by the Sponsor.

e. Subjects should be followed for 28 days after the last dose of study treatment to collect any AE/SAE information and perform a contraception check. This follow-up may be conducted at the study site or by phone.

f. Visit windows are based on telephone or clinic visit days relative to start of study treatment (Day 1).

g. **Cohort A:** Full physical examination (including weight and vital signs) results from the End of Study visit from B3461028 will be used for Day 0 baseline assessment for Study B3461045. If more than 30 days have elapsed, a brief physical examination must be performed on Day 0.

   Cohort B: A full physical examination is required on Day 0.

h. Brief physical examinations, including assessment of general appearance, and cardiovascular, respiratory, and gastrointestinal systems, are to be performed at clinic visits (Months 6, 12, 18, 24, 30, 36, 42, 48, 54). *For countries listed in Appendix 4.2 only: Brief physical examination including weight measurement will be performed at Month 3 visit.*

i. Measurement of height in centimeters (cm) will be performed at the Screening Day 0 visit.

j. 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.

k. **Cohort A:** Clinical laboratory testing includes serum chemistry, hematology, coagulation, urinalysis, and pregnancy testing. Coagulation (International normalized ratio [INR] and Prothrombin time [PT]) will be determined at the site's local laboratory. Subjects who already confirmed menopause with an FSH test in Study B3461028 do not need to repeat this test. The FSH test is applicable only to subjects newly fulfilling the 12 consecutive months of amenorrhea required to make the diagnosis of menopause.

   Cohort B: Clinical laboratory testing includes serum chemistry, hematology, coagulation, urinalysis, and pregnancy testing. Coagulation (International normalized ratio [INR] and Prothrombin time [PT]) will be determined at the site's local laboratory. FSH test may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during

the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

l. **Cohort A:** Clinical laboratory test results from Study B3461028 End of Study visit will be used for Day 0 of Protocol B3461045. If more than 30 days have elapsed between Study B3461028 End of Study visit and Day 0, then a new set of clinical laboratory tests must be performed prior to enrollment and randomization.

Cohort B: Clinical laboratory tests are required at Day 0 prior to study enrollment.

m. For female subjects of childbearing potential as defined in Section 4.3.1, at each telephone and clinic 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 case report form. Subjects will be instructed to continue use of birth control for at least 28 days after study participation. Subjects who have not followed contraception requirements as determined at the time of the post-study telephone call will be asked to confirm pregnancy status.

n. Subjects will be given a supply of tafamidis on Day 0 for self-administration at home beginning on Day 1 (ie, first dose). At telephone visits (Months 3, 9, 15, 21, 27, 33, 39, 45, 51, 57) supplies of tafamidis will be shipped to subjects from the clinical site by specialized IP courier. Tafamidis will not be dispensed if the protocol specified telephone call visit has not occurred. Subjects will return for clinic visits every 6 months (Months 6, 12, 18, 24, 30, 36, 42, 48, 54) for evaluation and will receive a supply of tafamidis for self-administration at home. Tafamidis will not be dispensed at clinic visits if the protocol specified clinic visit procedures have not been performed.

o. Subjects will self-administer study medication at home at the same time every day beginning on Day 1.

p. 12-lead ECG will be performed on an annual basis (every 12 months) at clinic visits Months 12, 24, 36, 48 and the Month 60 End of Study visit or Early Discontinuation visit. *For countries listed in Appendix 4.2 only: An additional ECG will be performed at the Month 3 visit.*

q. ECG will be performed only if the previous assessment occurred more than six months prior to the End of Study visit.

r. Sites will determine at each visit (telephone, clinic, end of study, or early discontinuation) whether the subject has been hospitalized (including the reason for hospitalization).

s. 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. 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.

t. In the event of early study discontinuation, the site staff will follow-up on the subject's vital status/transplant status 60 months after randomization/assignment date.

u. Only countries listed in Appendix 5 may screen/enroll subjects in Cohort B. Upon availability of Day -30 disease confirmation results, subjects in Cohort B may return to the study site for Day 0 visit procedures.

v. **Cohort A**: On Day 0, subjects in Cohort A will be blindly assigned to tafamidis meglumine 20 mg or 80 mg.

Cohort B: On Day 0, subjects in Cohort B will be assigned to open label tafamidis 61 mg (or tafamidis meglumine 80 mg if unavailable).

w. Cohort B only: Collect a genomic banked biospecimen. If missed, collect at the next available time point when biospecimens are being collected in conjunction with a subject visit.

x. Cardiac biomarkers NT-proBNP and Troponin I sample collection effective after Protocol Amendment 4. Study subjects enrolled prior to Protocol Amendment 4 are required to sign an updated informed consent prior to providing blood sample for cardiac biomarker assessment.

y. See Appendix 7 for Additional sample and banked biospecimen collection for newly enrolling subjects in specific countries. These samples will be used to support identification and characterization of serum, plasma, or urinary biomarkers of transthyretin amyloidosis. This collection introduced in Protocol Amendment 5 is relevant only to subjects participating in countries listed in Appendix 6.

1. INTRODUCTION

1.1. Indication

Pfizer is developing tafamidis, an oral small molecule, for the treatment of transthyretin amyloid diseases. Tafamidis has been demonstrated to stabilize transthyretin and is being developed for the treatment of ATTR-CM in patients with variant or wild-type TTR to reduce the combination of all-cause mortality and cardiovascular-related hospitalization.

Tafamidis is currently approved in the United States for treatment of cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization. Tafamidis is also approved for the treatment of ATTR-CM in Japan.

Tafamidis is currently approved for treatment of ATTR-PN in 41 countries and is commercially available in the following 26 countries: Argentina, Austria, Belgium, Brazil, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Israel, Italy, Japan, Lichtenstein, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Slovenia, Spain, Sweden and United Kingdom.

1.2. Background

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 (ATTR-PN) when the peripheral nerves are primarily affected and transthyretin amyloid cardiomyopathy (ATTR-CM) when the heart is primarily affected. Both ATTR-PN and ATTR-CM are associated with genetic variants of transthyretin but ATTR-CM may also occur in the absence of any genetic mutation, and may be due to wild-type TTR amyloid deposition.

ATTR-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.

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 ATTR-CM and therefore represent a disease modifying therapy.

Study B3461028 was a 30-month, Phase 3, double-blind, placebo-controlled, randomized, parallel-group trial designed to evaluate the efficacy, safety and tolerability of oral dosing of tafamidis meglumine 20 mg or 80 mg in comparison to placebo in subjects diagnosed with transthyretin cardiomyopathy and heart failure. The study enrolled 441 male and female subjects aged 18 to 90 years, with ATTR-CM due to either variant, or wild type TTR from sites in North and South America, the European Union, and Japan. The primary analysis included all-cause mortality and the frequency of cardiovascular-related hospitalizations and demonstrated a statistically significant reduction in the combination of all-cause mortality and frequency of cardiovascular-related hospitalizations compared to placebo. The preliminary safety data showed that tafamidis was generally well tolerated in this subject population and no new safety signals were identified.

The B3461045 protocol was designed as a long-term extension safety study for subjects who have completed 30 months of blinded treatment in Study B3461028. Given the positive results of the B3461028 study and the favorable benefit to risk profile there was a justification to provide patients with an option for early access to tafamidis. Consequently, the B3461045 study protocol was amended to include an additional cohort of patients with ATTR-CM who did not previously participate in the B3461028 parent study (Cohort B). The purpose of the additional cohort is to provide these patients early access to tafamidis, until local availability by prescription for the ATTR-CM indication. Additionally, a new formulation which is bioequivalent to tafamidis meglumine 80 mg has been developed and is presented as tafamidis 61 mg (as the free acid). This formulation, where available, will replace the tafamidis meglumine 80 mg dose after protocol amendment 3.

The current protocol describes a long-term safety extension study for subjects diagnosed with ATTR-CM who completed 30 months of participation in Study B3461028 (Cohort A) and subjects diagnosed with ATTR-CM who have not previously participated in the B3461028 (Cohort B).

1.3. Dose Rationale

At enrollment, subjects in Cohort A were assigned to 20 mg and 80 mg tafamidis meglumine in a blinded manner. At enrollment, subjects in Cohort B will be assigned to open label 61 mg tafamidis (or 80 mg tafamidis meglumine if unavailable).

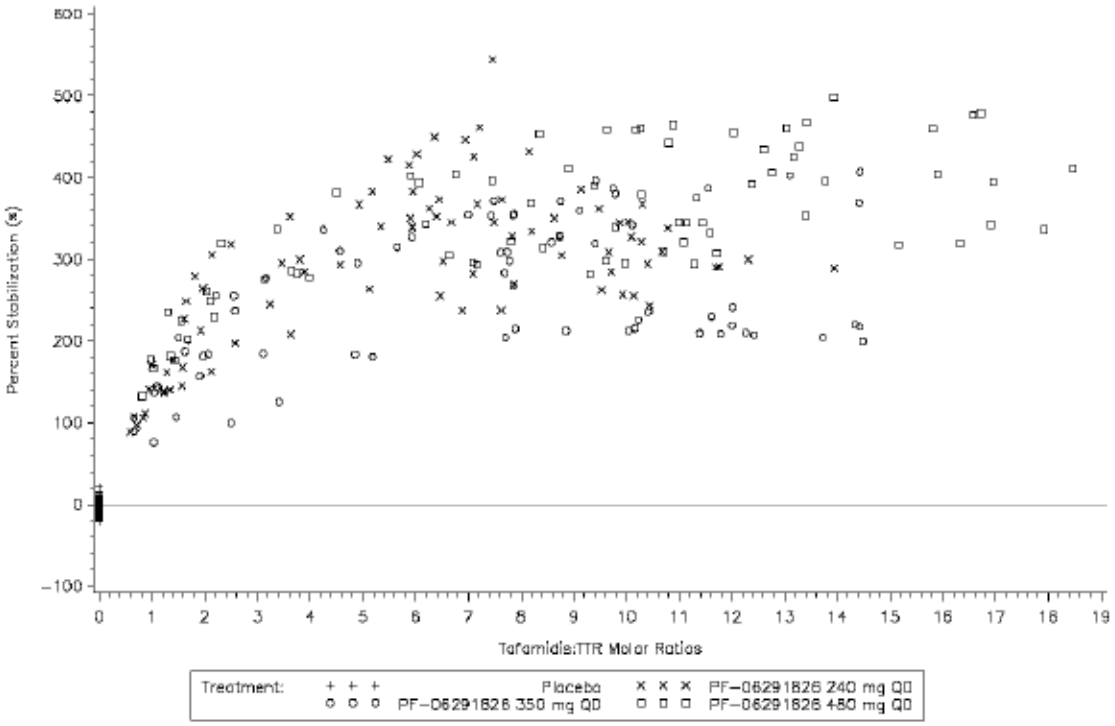
The 20 mg dose of tafamidis has been previously studied in ATTR-PN; it has been shown to be effective in delaying progression of symptomatic ATTR-PN disease and is the approved dose. Both the 20 mg and 80 mg doses of tafamidis were studied under Protocol B3461028, a multinational, multicenter, double-blind randomized placebo-controlled Phase 3 clinical trial to assess the efficacy, safety and tolerability of tafamidis in subjects with TTR-cardiomyopathy (ATTR-CM).

The rationale for the 80 mg dose was based on results from Study B3461040, which was a Phase 1, randomized, double-blind, crossover, ascending dose-escalation study 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 9 healthy adult Asian men.

The TTR percent stabilization data from Study B3461040 (Figure 1) suggest that a plateau is achieved as the molar ratio (MR) of tafamidis: TTR plasma concentration 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 percent 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 once daily (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 percent stabilization.

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



Source: B3461040 CSR Figure 14.4.7.2.1.

TTR percent stabilization data indicate increased stabilization at the 80 mg dose versus the 20 mg dose and the results from Study Fx-005 support the 20 mg dose in ATTR-PN. The 20 mg dose will provide additional safety data in subjects with TTR mutations. The 80 mg dose is approaching maximal TTR percent stabilization.

Results from Study B3461054 demonstrated that tafamidis may be administered orally without regard to food. In addition, steady-state evaluation of data from Study B3461056 demonstrated the bioequivalence of the 61 mg tafamidis soft gel capsule to the 4 x 20 mg tafamidis meglumine soft gel capsules.

In light of the similarity in the clinical efficacy and safety profile of tafamidis meglumine 20 mg and 80 mg observed in Study B3461028 and biomarker data that suggest some increased benefit of the 80 mg dose compared to the 20 mg dose, tafamidis meglumine 80 mg is the recommended dose for patients with ATTR-CM. Patients who are not able to tolerate the 80 mg dose may be down-dosed to 20 mg tafamidis meglumine.

Tafamidis, as the meglumine salt in gelatin capsules was used to date in Studies B3461028 and B3461045. The new formulation of 61 mg tafamidis as the free acid in a single gelatin capsule is being introduced to patients to provide the higher dose in a single capsule. Complete information for this compound may be found in the single reference safety document (SRSD), which for this study is the Investigator's Brochure (IB).

Banked biospecimens will be collected for the purpose of conducting research; specific uses are described in the Banked Biospecimens section. Comparing the deoxyribonucleic acid (DNA), ribonucleic acid (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 subjects in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/genomic/biomarker analyses and retaining them in the Biospecimen Banking System (BBS) make it possible to better understand the investigational product's mechanism of action and to seek explanations for differences in, for example, exposure, tolerability, safety, and/or efficacy not anticipated prior to the beginning of the study. Banked biospecimens retained in the BBS also can be used in research on ATTR-CM. Providing these biospecimens is a required study activity for study sites and subjects, unless prohibited by local regulations or ethics committee (EC) decision.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary Objectives:

- To obtain additional, long-term, safety data for tafamidis in subjects with transthyretin amyloid cardiomyopathy (ATTR-CM).
- To provide investigational product, tafamidis, to enrolled subjects until local availability by prescription for the ATTR-CM indication.

2.2. Endpoints

Primary Endpoints

Safety as measured by:

- All-cause mortality.
- Incidence of treatment-emergent adverse events.

Other Endpoints

- Cardiovascular-related mortality.
- Frequency of all-cause hospitalization.
- Frequency of cardiovascular-related hospitalization (including heart failure, arrhythmia, myocardial infarction, stroke and other cardiovascular-related events).
- Change from baseline at each visit in Kansas City Cardiomyopathy Questionnaire Overall Summary score, domain scores (Physical limitation, Symptom stability, Symptom frequency, Symptom burden, Total symptom, Self-efficacy, Social limitation, and Quality of life), and Clinical summary score.
- New York Heart Association classification at each visit.
- Change from baseline in Body Mass Index/modified Body Mass Index at each visit.
- Change from baseline in NT-proBNP concentration at each visit.
- Change from baseline in Troponin I concentration at each visit.
- Assessment of physical examinations, use of concomitant medications, electrocardiograms (ECGs), clinical laboratory testing, vital signs at each visit.

For those serious adverse events (SAEs) that are handled as disease-related endpoints (which may include death), an external data monitoring committee (E-DMC) will conduct unblinded reviews on a regular basis throughout the trial (Data Monitoring Committee).

3. STUDY DESIGN

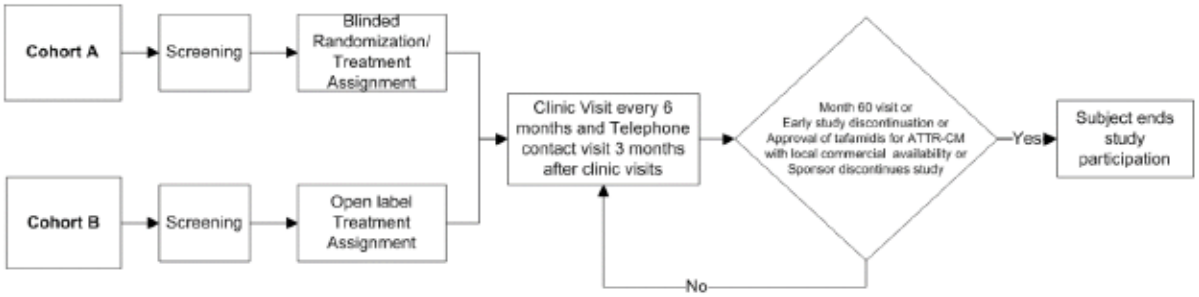
This is a Phase 3, open-label long-term extension safety study designed to obtain additional safety data for tafamidis meglumine 20 mg and 80 mg (or tafamidis 61 mg where available), and to continue to provide enrolled subjects with tafamidis for up to 60 months, or until subject has access to tafamidis for ATTR-CM via prescription, whichever occurs first. The study will also end before 60 months if the sponsor discontinues the study. Subjects withdrawn from the study due to commercial access to prescription tafamidis in their

respective countries will be considered study completers. The decision to withdraw subjects for transition to commercial tafamidis will be made by the sponsor.

Eligible study participants will be enrolled in 2 cohorts:

- Cohort A – Subjects diagnosed with ATTR-CM who completed 30 months of participation in Study B3461028.
- Cohort B – Subjects diagnosed with ATTR-CM who have not previously participated in Study B3461028 (Appendix 5).

Figure 2. Flowchart of Study Participation



Subjects in Cohort A will be assigned to open label treatment after protocol amendment 3.

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 participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

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

4.1. Inclusion Criteria

4.1.1. Cohort A Inclusion Criteria

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

1. Male and female subjects with TTR amyloid cardiomyopathy who have completed 30 months of study treatment on Protocol B3461028.
2. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.
3. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

4. Male subjects able to father children and female subjects of childbearing potential and at risk for pregnancy must agree to use 2 highly effective methods of contraception throughout the study and for at least 28 days after the last dose of assigned treatment.

   Female subjects who are not of childbearing potential (ie, meet at least 1 of the following criteria):

   - Have undergone a documented hysterectomy and/or bilateral oophorectomy;
   - Have medically confirmed ovarian failure; or
   - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by having a serum follicle- stimulating hormone (FSH) level confirming the post-menopausal state.

   All other female subjects (including females with tubal ligations) will be considered to be of childbearing potential.

4.1.2. Cohort B Inclusion Criteria

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

1. Male or female subject of at least 18 years of age (or the minimum country specific age of consent if >18) and participates at a study site in an eligible country listed in Protocol Appendix 5.
2. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.
3. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
4. A female subject is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

   - Is not a Woman of Childbearing Potential (WOCBP) (see definition Section 4.3.1).

   OR

   - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year) (see Section 4.3) during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any study intervention. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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

5. Documentation of the genetic testing for transthyretin amyloidosis (ie, original laboratory result, or copy).

6. Documentation of diagnosis and criteria used (eg, congestive heart failure and scintigraphy with tracer *eg, 99mTC DPD [99mTC 3,3 diphosphono 1,2 propano dicarboxylic acid], 99mTC PYP [Pyrophosphate] and also 99mTC HMDP [hydroxymethylene diphosphonate]* or Congestive heart failure and presence of amyloid deposits in biopsy tissue, *eg, fat aspirate, salivary gland, median nerve connective tissue sheath, or cardiac [amyloid demonstrated per appropriate stain such as Congo red or alcian blue stain]).*

7. Documentation that primary (light chain) amyloidosis disease has been evaluated and ruled out (ie, original laboratory result, or copy).

8. Evidence of NYHA classification I, II, III, or IV.

4.2. Exclusion Criteria

4.2.1. Cohort A Exclusion Criteria

Subjects in Cohort A with any of the following characteristics/conditions will not be included in the study:

1. Chronic use of diflunisal, TTR stabilizer, tauroursodeoxycholate, doxycycline, digitalis, patisiran, calcium channel blockers, investigational drug(s) or other experimental interventions, other than tafamidis, independently or as part of a study within 30 days prior to enrollment or inotersen within 6 months prior to enrollment.

2. Use of certain non-steroidal anti-inflammatory drugs (NSAIDs) [Section 5.8.1].

3. Liver and/or heart transplant, or implanted cardiac mechanical assist device.

4. Pregnant females (or planning to become pregnant during the study interval); breastfeeding females; male subjects with partners currently pregnant.

5. Require initiation of treatment with calcium channel blockers.

6. Urinary retention requiring chronic self-catheterization.

7. Breach of compliance with treatment/significant protocol violations during conduct of B3461028 for which the subject was accountable.

8. Subjects who are investigational site staff members directly involved in the conduct of the study 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 study.

9. 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 that 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.

4.2.2. Cohort B Exclusion Criteria

Subjects in Cohort B with any of the following characteristics/conditions will not be included in the study:

1. Chronic use of diflunisal, TTR stabilizer, tauroursodeoxycholate, doxycycline, digitalis, patisiran, calcium channel blockers, investigational drug(s) or other experimental interventions, other than tafamidis, independently or as part of a study within 30 days prior to enrollment, or inotersen within 6 months prior to enrollment.

2. Use of certain non-steroidal anti-inflammatory drugs (NSAIDs) [Section 5.8.1].

3. Liver and/or heart transplant, or implanted cardiac mechanical assist device.

4. Require initiation of treatment with calcium channel blockers.

5. Urinary retention requiring chronic self-catheterization.

6. 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.

7. Subjects who are investigational site staff members directly involved in the conduct of the study 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 study.

8. 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 that 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.

4.3. Lifestyle Guidelines

All female subjects who are of childbearing potential as applicable to the study who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 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 an appropriate method of contraception for the individual subject from the permitted list of contraception methods (see below) and will confirm that the subject has been instructed in its 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 highly effective contraception consistently and correctly and document the conversation and the subject's affirmation in the subject's chart (subjects needs to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the 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. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device (IUD).
3. Intrauterine hormone-releasing system (IUS).
4. Bilateral tubal occlusion.
5. Vasectomized partner:
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.
6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - oral;
    - intravaginal;
    - transdermal;

- injectable.

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

   - Oral;

   - Injectable.

8. Sexual abstinence:

   - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

4.3.1. Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are <u>not</u> considered WOCBP:

1. Premenopausal female with 1 of the following:

   - Documented hysterectomy;

   - Documented bilateral salpingectomy;

   - Documented bilateral oophorectomy.

   For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female:

   - A postmenopausal state is defined as age 60 years or older or no menses for 12 months without an alternative medical cause.

- A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT).

- Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

4.4. Sponsor's Qualified Medical Personnel

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

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 numbers, contact information for the investigational site, and contact details for a contact center 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 subject's participation in the study.

The contact number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should be used only 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 the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigational site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonization (ICH) guidelines investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

5.1. Allocation to Treatment

Investigators will confirm the eligibility of each subject to meet inclusion/exclusion criteria. Subject eligibility for participation in the treatment phase of the protocol will be determined following the assessments during the Screening 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 enrolled into the study.

Each subject in Cohort A who has signed the informed consent document (ICD) will be assigned the same subject identification number from the parent study B3461028 by an Interactive Response Technology (IRT) system. Each subject in Cohort B will be assigned a new subject identification number by the Interactive Response Technology (IRT) system.

Allocation of subjects to treatment groups will proceed through the use of an IRT system unless otherwise directed by the Sponsor to ensure patient safety and study continuity. The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, the subject number and the date of birth of the subject. The site personnel will then be provided with a treatment assignment and dispensable unit (DU) or container number. The IRT System will provide a confirmation report containing the subject number and DU or container number assigned.

Clinic visits will be at 6-month intervals (Month 6, 12, 18 etc.). Subjects must return for their appointment before their study drug supply is exhausted. Subjects must bring all of their study medication and their Subject Daily Dosing Diary to each clinic visit. The site will collect all study medication dispensed at the previous visit and dispense a new set of study medication and a Subject Daily Dosing Diary to the subject.

There is a 24-hour-a-day, 365-days-a-year IRT helpdesk available for any questions or issues. The study specific IRT reference manual will provide the contact information and further details on the use of the IRT system.

Note: The IRT is the source of the subject number. The IRT system will provide the subject number at the end of the first IRT subject transaction.

5.1.1. Cohort A Treatment Assignment

There will be treatment assignment stratification by TTR genotype (variant or wild-type) only for Cohort A.

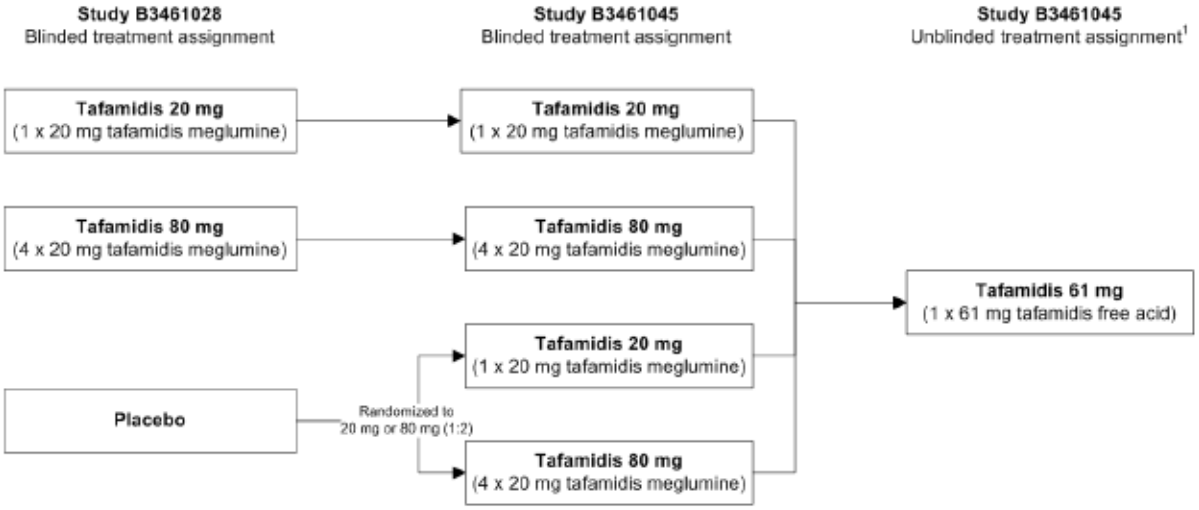
At enrollment, subjects in Cohort A were assigned to blinded active treatment in this study; tafamidis meglumine 20 mg or 80 mg once daily, in addition to standard of care (eg, diuretics) for up to 60 months based on the following:

- Subjects receiving tafamidis meglumine 20 mg or 80 mg in Study B3461028 continue the same blinded treatment assignment.
- Subjects assigned to placebo in Study B3461028 will be randomized (1:2) to blinded tafamidis meglumine 20 mg or 80 mg. Subjects assigned to placebo in Study B3461028 and randomized to tafamidis meglumine 80 mg will be permitted one blinded dose-reduction to 20 mg for adverse events related to tolerability.

Subjects in Cohort A will be assigned to open label treatment after protocol amendment 3.

Subjects receiving tafamidis meglumine 20 mg or 80 mg will be assigned to tafamidis 61 mg, once daily, in addition to standard of care (eg, diuretics), for up to 60 months. Subjects will be assigned to tafamidis meglumine 80 mg in regions where 61 mg tafamidis is unavailable.

Figure 3. Study Treatments



[1]One permanent dose reduction to 20 mg tafamidis meglumine is permitted for adverse events related to tolerability; Subjects will be assigned to 80 mg tafamidis meglumine in regions where 61 mg tafamidis is unavailable

5.1.2. Cohort B Treatment Assignment

At enrollment, subjects in Cohort B will be assigned to open label 61 mg tafamidis once daily, in addition to standard of care (eg, diuretics), for up to 60 months. One dose reduction to 20 mg tafamidis meglumine will be permitted for adverse events related to tolerability. Subjects will be assigned to 80 mg tafamidis meglumine in regions where 61 mg tafamidis is unavailable.

5.2. Breaking the Blind

Subjects in Cohort A will be blinded to treatment assignment at enrollment into the study. Treatment assignments will remain blinded to the subject and investigator until assigned to open label treatment as described in Section 5.1.1.

The study treatment assignment will be subject and investigator blinded as to dose. At the initiation of the study, the study site will be instructed on the method for 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, study clinician or the medical 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 a serious adverse event (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.

When the blinding code is broken, the reason must be fully documented and entered on the case report form (CRF). Individual subjects whose blind is broken will be discontinued from the study as described in Section 6.2.4.

5.3. Subject Compliance

Subjects will be instructed to take the medication on a daily basis. They will also be instructed to return all of their study medication to the study site, including used and unused study medication, 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 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. Subjects will be considered to be adherent to the dosing requirements of the study if they have taken the required daily dose of study medication per day on at least 80% of the days of study participation.

5.4. Investigational Product Supplies

Cohort A blinded treatment assignment:

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 matching blinded placebo plus 1 capsule of blinded tafamidis meglumine 20 mg, 2 capsules of matching blinded placebo plus 2 capsules of blinded tafamidis meglumine 20 mg, or 4 capsules of blinded tafamidis meglumine 20 mg. (Table 1).

Cohort A and B open label treatment assignment:

After protocol amendment 3, all subjects will be assigned to open label treatment. Each dose of tafamidis 61 mg or tafamidis meglumine 20 mg consists of 1 capsule. Each dose of tafamidis meglumine 80 mg consists of 4 capsules. (Table 1).

Table 1. Investigational Product Supplies

Dosage Level (Compound)	Appearance	Number of Capsules Per Day (Dose)
Tafamidis meglumine 20 mg (PF-06291826-83) - blinded	Yellow, oblong soft gelatin capsules	1 (Tafamidis meglumine 20 mg capsule) 3 (Placebo capsules)
Tafamidis meglumine 80 mg (PF-06291826-83) - blinded	Yellow, oblong soft gelatin capsules	4 (Tafamidis meglumine 20 mg capsules)
Tafamidis free acid 61 mg (PF 06291826-00) - open	Reddish brown, oblong soft gelatin capsules	1 (Tafamidis free acid 61 mg capsule)
Tafamidis meglumine 20 mg (PF 06291826-83) - open	Yellow, oblong soft gelatin capsules	1 (Tafamidis meglumine 20 mg capsule)
Tafamidis meglumine 80 mg (PF 06291826-83) - open	Yellow, oblong soft gelatin capsules	4 (Tafamidis meglumine 20 mg capsules)

5.4.1. Dosage Form(s) and Packaging

Cohort A Blinded Dosage Form and Packaging:

Blinded PF-06291826 (tafamidis meglumine) will be provided as soft gel capsules for oral administration (Table 1). The capsules will be supplied in separate blister cards and labeled according to local regulatory requirements.

Tafamidis meglumine 20 mg in soft gel capsules will be packaged as 8 tri-fold investigational product wallets in each carton, with each wallet labeled 1 through 8. Each investigational product wallet will be packaged with enough medication for 15 days of dosing.

Subjects will be dispensed 1 carton containing 8 investigational product wallets. This will provide enough investigational product for each 3-month dosing period plus 2 extra investigational product wallets to allow for flexibility in clinic visit scheduling (total of 120 days supply).

Subjects should be instructed to only dose from 1 investigational product wallet each day. Subjects should take 4 capsules one time per day with water. Subjects should be instructed to complete dosing from one investigational product wallet prior to starting dosing from the next consecutively numbered investigational product wallet.

Cohort A & B Open Label Dosage Form and Packaging:

After protocol amendment 3, study treatment will be provided as soft gel capsules for oral administration (Table 1). The capsules will be supplied in bottles and labeled according to local regulatory requirements.

For open-label treatment assignment, subjects will be dispensed 1 carton at each visit containing either:

- 3 x bottles of tafamidis 61 mg capsules (40 count per bottle, 120 days supply per carton); or
- 3 x bottles of tafamidis meglumine 20 mg capsules (40 count per bottle, 120 days supply per carton); or
- 12 x bottles of tafamidis meglumine 20 mg capsules (40 count per bottle, 120 days supply per carton).

5.4.2. Preparation and Dispensing

Investigational product will be dispensed at the Screening visit (Day 0) and at every specified telephone or clinic visit thereafter using an IRT system. A qualified staff member will dispense the investigational product cartons provided.

Subjects will be given a supply (Section 5.4.1) of tafamidis on Day 0 for self-administration at home beginning on Day 1 (ie, first dose). At telephone visits (Months 3, 9, 15, 21, 27, 33, 39, 45, 51, 57) supplies of IP will be shipped to subjects from the clinical site by a specialized IP courier. Any IP shipped directly to subject following a telephone visit will be dispensed at the site per the process listed above and monitored for temperature during shipping process through delivery. Subjects will return for clinic visits every 6 months (Months 6, 12, 18, 24, 30, 36, 42, 48, 54) for evaluation and will receive a supply of IP for self-administration at home.

IP will not be dispensed if the protocol specified telephone visit procedures have not been performed. Details of procedures for shipping by specialized IP courier will be included in the IP shipping reference guide. IP will not be dispensed at clinic visits if the protocol specified clinic visit procedures have not been performed.

5.5. Administration

Cohort A blinded treatment: Subjects will be instructed to take 4 capsules per day of blinded therapy 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.

Cohort A & B open label treatment: Subjects will be instructed to take 1 capsule per day from bottle, or 4 capsules per day for subjects on tafamidis meglumine 80 mg 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 each day. 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 as instructed above at the next planned dosing time.

Similarly, if multiple doses from previous days 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.

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). 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.

5.5.1. Dose-reduction

A one-time dose reduction to 20 mg tafamidis meglumine will be permitted for subjects after switching to 61 mg tafamidis.

Cohort A blinded dose reduction

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 request blinded treatment re-assignment to a lower dose. Only subjects assigned to 80 mg tafamidis in B3461045 after 30 months of placebo in Study B3461028 will be permitted one blinded dose-reduction to 20 mg.

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 in Study B3461045 after 30 months of placebo in Study B3461028, then the re-assignment will be to 20 mg. All other subjects will be maintained on the previously assigned dose but will still receive a new container number in order to maintain the blind.

If tolerability issues continue after the blinded re-assignment, the investigator 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 60 months after randomization into B3461045.

Cohort A & B open label dose reduction

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 request treatment re-assignment to a lower dose. All subjects will be permitted one open label dose-reduction to 20 mg.

The site personnel will enter the subject's study specific identification (SSID) number into the IRT system and request an open label dose reduction. The IRT system will provide a new container number for open label treatment re-assignment for this subject.

If tolerability issues continue after the re-assignment, the investigator 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 60 months after randomization into B3461045.

5.6. Investigational Product 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 products should be stored in accordance with the clinical supply label.

Investigational product should be stored in its original package and should be protected from light. Site systems must be capable of measuring and documenting (eg, 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 that ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (eg, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to the storage conditions as described in the clinical supply label, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor. Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor 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 products.

5.7. Investigational Product Accountability

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All study drugs will be accounted for using a drug accountability form/record. At each scheduled clinic visit, beginning at the Month 6 visit, subjects will return used and unused investigational product 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 compliance.

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 study 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 Treatment(s)

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

Concomitant Treatment is defined as ongoing or initiated at any time on or after Day 1 of the study through the final study visit. Concomitant treatments include any substance ingested, injected, absorbed, inhaled, or that 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.

5.8.1. Prohibited Therapies

Use of NSAIDs other than those noted below was prohibited during participation in parent study B3461028 and is prohibited during Study B3461045. Some NSAIDs, like diflunisal, can bind to the thyroxine binding sites on transthyretin (Almeida 2004).[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, inotersen, or patisiran during the study is prohibited.
3. 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).[2,5,4]

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. There may be circumstances, such as a constraint on travel for health-related reasons, in which 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 the visit windows. Visit windows are based on telephone or clinic visit days relative to start of study treatment (Day 1).

6.1. Screening Visit

6.1.1. Screening Visit Cohort A (Day 0)

Screening Visit (Day 0) is the Month 30 End of Study visit and last day of treatment for Study B3461028. Study procedures and assessments will be performed once per subject and the protocol-specified data will be reported separately for each study. Subjects providing consent and fulfilling the inclusion/exclusion criteria will be enrolled, randomized, and dispensed study medication for Study B3461045 at the same visit. Subjects will be instructed to start self-administration of tafamidis the following day (Day 1).

If more than 30 days have elapsed from the B3461028 End of Study visit, then vital signs, a brief physical examination, clinical laboratory tests, contraception check, concomitant medications, adverse event reporting must be performed on Day 0 prior to enrollment.

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

The following procedures will be conducted during the Screening/Day 0 visit:

- All inclusion and exclusion criteria will be reviewed to ensure eligibility for participation in this study [Study B3461045 only].
- Demography (date of birth, age, gender and race) [Study B3461045 only].
- Complete medical history (including history of heart failure) [Study B3461045 only].
- Full physical examination including weight and height measurements will be performed. If more than 30 days have elapsed from the B3461028 Month 30 End of Study visit, then a brief physical examination must be performed on Day 0.
- Measure vital signs (systolic and diastolic blood pressure supine and standing, pulse rate supine and standing, respiration rate, and body temperature).

- Single 12-lead ECG - perform ECG prior to any blood collection or blood pressure measurements.
- Collect blood, and urine samples for the following clinical laboratories. If more than 30 days have elapsed from the B3461028 Month 30 End of Study visit, then a new set of clinical laboratory tests must be performed prior to enrollment and randomization.
  - Hematology;
  - Serum Chemistry;
  - Coagulation (International normalized ratio [INR], Prothrombin time [PT]);
  - Urinalysis;
  - Urine pregnancy test – for women of childbearing potential;
  - Follicle-stimulating hormone (FSH) test – for female subjects of non-childbearing potential who have not had a hysterectomy, bilateral oophorectomy, or medically confirmed ovarian failure. Subjects who already confirmed menopause with an FSH test in Study B3461028 do not need to repeat this test. The FSH test is applicable only to subjects newly fulfilling the 12 consecutive months of amenorrhea required to make the diagnosis of menopause.
- Contraception check.
- New York Heart Association (NYHA) classification.
- Administer Kansas City Cardiomyopathy Questionnaire.
- Documentation of vital status and transplant or cardiac mechanical assist device status.
- Documentation of concomitant medications.
- Adverse event reporting.
- Treatment allocation/Randomization and dispense blinded investigational product. [Study B3461045 only].
- Instructions to subjects to self-administer blinded investigational product at home at the same time every day beginning on Day 1. [Study B3461045 only].

6.1.2. Screening Visit Cohort B (with disease documentation) (Day 0)

Subjects providing consent and fulfilling the inclusion/exclusion criteria will be enrolled and dispensed study medication for Study B3461045 at the same visit. Subjects will be instructed to start self-administration of tafamidis the following day (Day 1).

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

The following procedures will be conducted during the Screening/Day 0 visit:

- All inclusion and exclusion criteria will be reviewed to ensure eligibility for participation in the study.
- Complete Demography.
- Complete medical history (including history of heart failure).
- Full physical examination including weight and height measurements will be performed.
- Measure vital signs (systolic and diastolic blood pressure supine and standing, pulse rate supine and standing, respiration rate, and body temperature).
- Single 12-lead ECG - perform ECG prior to any blood collection or blood pressure measurements.
- Collect blood, and urine samples for the following clinical laboratories:
  - Hematology;
  - Serum Chemistry;
  - Coagulation (International normalized ratio [INR], Prothrombin time [PT]);
  - NT-proBNP and troponin I;
  - Urinalysis;
  - Urine pregnancy test – for women of childbearing potential;
  - Follicle-stimulating hormone (FSH) test – may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment (Section 4.3.1).

- Collect banked biospecimen.
- Contraception check.
- Administer Kansas City Cardiomyopathy Questionnaire.
- New York Heart Association (NYHA) classification.
- Collect documentation of the genetic testing for transthyretin amyloidosis (ie, original laboratory result, or copy). The original laboratory result, or copy will be part of the source documentation.
- Collect documentation of diagnosis and criteria used (eg, congestive heart failure and scintigraphy with tracer eg, 99mTC DPD [99mTC 3,3 diphosphono 1,2 propano dicarboxylic acid], 99mTC PYP [Pyrophosphate] and also 99mTC HMDP [hydroxymethylene diphosphonate] or 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]). The original laboratory result, or copy will be part of the source documentation.
- Collect documentation that primary (light chain) amyloidosis disease has been evaluated and ruled out (ie, original laboratory result, or copy). The original laboratory result, or copy will be part of the source documentation.
- Documentation of vital status and transplant or cardiac mechanical assist device status.
- Documentation of concomitant medications.
- ***For countries listed in Appendix 6:*** *Additional sample collection procedures will be performed at Screening (Day 0). See Appendix 7 for procedure details.*
- Adverse event reporting.
- Treatment allocation and dispense blinded investigational product.
- Instructions to subjects to self-administer blinded investigational product at home at the same time every day beginning on Day 1.

6.1.3. Screening Visit (Day -30) Cohort B Subjects without Documentation of Diagnosis

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

The following procedures will be conducted during the Screening/Day -30 visit:

- All inclusion and exclusion criteria will be reviewed to ensure eligibility for participation in the study.

- Complete Demography.
- Complete Medical History (including history of heart failure).
- Collect samples for disease diagnosis:
  - Genotyping;
  - Serum and urine test for primary light chain amyloidosis;
  - Tissue Biopsy.
- Documentation of vital status and transplant or cardiac mechanical assist device status.
- Documentation of concomitant medications.
- Adverse event reporting.

6.1.4. Screening Visit (Day 0) Cohort B (without disease documentation)

The following procedures will be conducted during the Screening/Day 0 visit:

All inclusion and exclusion criteria will be reviewed to ensure eligibility for participation in this study.

- Full physical examination including weight and height measurements will be performed.
- Measure vital signs (systolic and diastolic blood pressure supine and standing, pulse rate supine and standing, respiration rate, and body temperature).
- Single 12-lead ECG perform ECG prior to any blood collection or blood pressure measurements.
- Collect blood, and urine samples for the following clinical laboratories:
  - Hematology;
  - Serum Chemistry;
  - Coagulation (International normalized ratio [INR], Prothrombin time [PT]);
  - NT-proBNP and troponin I;
  - Urinalysis;
  - Urine pregnancy test – for women of childbearing potential;

  - Follicle-stimulating hormone (FSH) test – may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment (Section 4.3.1).

- Collect banked biospecimen.
- Contraception check.
- New York Heart Association (NYHA) classification.
- Administer Kansas City Cardiomyopathy Questionnaire.
- Documentation of vital status and transplant or cardiac mechanical assist device status.
- Documentation of concomitant medications.
- ***For countries listed in Appendix 6:*** *Additional sample collection procedures will be performed at Screening (Day 0). See Appendix 7 for procedure details.*
- Adverse event reporting.
- Treatment allocation and dispense investigational product.
- Instructions to subjects to self-administer blinded investigational product at home at the same time every day beginning on Day 1.

6.2. Study Period

The following chronology of activities is suggested for clinic visits:

- ECG – Perform ECG prior to vital sign and blood specimen collection.
- Vital Signs – Obtain blood pressure/pulse rate prior to blood specimen collection.
- Blood sample collection for clinical laboratories.

All other procedures should be obtained after blood specimen collections, unless sampling is determined by the study personnel to potentially impact the results.

6.2.1. Day 1

Subjects will self-administer investigational product at home.

6.2.2. Telephone Visits (Months 3, 9, 15, 21, 27, 33, 39, 45, 51, 57) ±2 Weeks

The clinical site will contact the subject by telephone to inquire about any adverse effects and their health status since the previous clinic visit. Telephone visit procedures may also be performed at the study site.

- The site will contact the subject by phone at a time agreed with the subject to collect the following information since the clinic visit:
  - Documentation of concomitant medications;
  - Adverse events reporting;
  - Hospitalization determination. Sites will determine whether the subject has been hospitalized and the reason for hospitalization;
  - Contraception check;
  - Documentation of vital status and transplant or cardiac mechanical assist device status.
- At the end of the phone call, the next clinic appointment will be confirmed and the subject will be reminded to record adverse events and medication use in the Subject Daily Dosing Diary. The subject will be reminded to return to the clinic with all dispensed study medication.
- Study site will dispense investigational product by specialized IP courier. The IP courier will also collect all previously dispensed (used and unused) investigational product from the subject and return to the site for accountability.
- ***For countries listed in Appendix 4.2:*** *subjects will be required to return to the study site at Month 3. Telephone visit procedures will be performed. The following additional procedures will also be performed at the Month 3 visit:*
  - *Brief physical examination including weight measurement;*
  - *Collect all dispensed (used and unused) investigational product;*
  - *Single 12-Lead ECG - perform ECG prior to any blood collection or blood pressure measurements;*
  - *Measure vital signs (systolic and diastolic blood pressure supine and standing, pulse rate supine and standing, respiration rate, and body temperature);*
  - *Collect blood and urine samples for the following clinical laboratories:*
    - *Hematology;*

- *Serum Chemistry;*
- *Coagulation (INR, PT);*
- *NT- proBNP and troponin I;*
- *Urinalysis.*

- *Urine pregnancy test – for women of childbearing potential.*
- *Administer Kansas City Cardiomyopathy Questionnaire.*
- *NYHA classification.*
- *Record capsule count for dosing adherence.*
- *Dispense blinded investigational product.*

6.2.3. Clinic Visits (Months 6, 12, 18, 24, 30, 36, 42, 48, 54) ±2 Weeks

The following procedures will be performed for all subjects at clinic visits:

- Brief physical examination including weight measurement.
- Collect all dispensed (used and unused) investigational product.
- Single 12-Lead ECG - perform ECG prior to any blood collection or blood pressure measurements (To be performed annually at Months 12, 24, 36, 48 or early discontinuation).
- Measure vital signs (systolic and diastolic blood pressure supine and standing, pulse rate supine and standing, respiration rate, and body temperature).
- Collect blood and urine samples for the following clinical laboratories:
  - Hematology;
  - Serum Chemistry;
  - Coagulation (INR, PT);
  - NT-proBNP and troponin I;
  - Urinalysis;
  - Urine pregnancy test – for women of childbearing potential.
- Administer Kansas City Cardiomyopathy Questionnaire.

- NYHA classification.
- Contraception check.
- Documentation of concomitant medications.
- Record capsule count for dosing adherence.
- Adverse event reporting.
- Hospitalization determination. Sites will determine whether the subject has been hospitalized and the reason for hospitalization.
- Documentation of vital status, transplant or cardiac mechanical assist device status.
- Dispense blinded investigational product.
- Schedule a date and time for the next telephone visit.

6.2.4. End of Study Visit (Month 60) ±2 weeks or Early Study Discontinuation

The following procedures will be performed for all subjects at the Month 60 visit or at the time of Early Study Discontinuation:

- Full physical examination including weight measurement.
- Collect all dispensed investigational product.
- Single 12-Lead ECG - perform ECGs prior to any blood collection or blood pressure measurements. ECG will be performed only if the previous assessment occurred more than six months prior to the End of Study visit.
- Measure vital signs (systolic and diastolic blood pressure supine and standing, pulse rate supine and standing, respiration rate, and body temperature).
- Contraception check.
- Collect blood and urine samples for the following:
  - Hematology;
  - Serum Chemistry;
  - Coagulation (INR, PT);
  - NT-proBNP and troponin I;

  - Urinalysis;
  - Urine pregnancy test – for women of childbearing potential.
- Kansas City Cardiomyopathy Questionnaire.
- NYHA classification.
- Documentation of concomitant medications.
- Record capsule count for dosing adherence.
- Adverse event reporting.
- Hospitalization determination.
- Documentation of vital status, transplant or cardiac mechanical assist device status.
- Schedule date and time for the post-study follow-up visit.

6.3. Post-study Follow-up Visit

Subjects should be followed for 28 days after the last dose of Study Treatment to collect any AE/SAE information and perform a contraception check. This post-study follow-up can be conducted at the study site or by telephone. Subjects who have not followed contraception requirements as determined at the time of the post-study telephone call will be asked to confirm pregnancy status.

The following information will be collected:

- Adverse event reporting (see Section 8).
- Contraception check.

6.4. 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.

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 or a 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 60 months following the Screening visit. The investigator should inquire about the reason for withdrawal, request that the subject return for a final study visit (if applicable) and to 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 60 months after Screening. 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.

6.4.1. 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/enrollment in the study. 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 60 months following the Screening 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 the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or 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 manner.

7.1. Safety Assessments

7.1.1. Medical History

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

7.1.2. Physical Examination and Height Measurements

All subjects will undergo a full physical examination at the Screening visit and the End of Study or Early Discontinuation Visit, including assessment of the following body systems:

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

Brief physical examinations, including assessment of general appearance, cardiovascular, respiratory, and gastrointestinal systems, are to be performed at all clinic visits (Months 6, 12, 18, 24, 30, 36, 42, 48, 54). *Brief physical examination and weight measurement will also be performed at Month 3 (Countries listed in Appendix 4.2).*

Measurement of height in centimeters (cm) will be performed at the Screening visit only.

7.1.3. Vital Signs

Vital signs (including body temperature, systolic and diastolic blood pressure, pulse rate and respiration rate) will be assessed and recorded at the Screening visit, at every clinic visit, and at the End of Study/Early Discontinuation visit. *Vital Signs will also be assessed at Month 3 (Countries listed in Appendix 4.2).*

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 is acceptable, although when performed 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.

7.1.4. Electrocardiogram

A 12-lead electrocardiogram (ECG) will be performed for all subjects at Screening and annual visits at Months 12, 24, 36, 48, 60 or early termination visit. *A 12-lead ECG will also be performed at Month 3 (Countries listed in Appendix 4.2).* Where possible, ECGs will be performed prior to blood pressure or pulse measurements or blood collection. All scheduled ECGs should be performed after the subject has rested quietly for at least 5 minutes in a supine position.

The following ECG parameters will be assessed: PR, RR, QRS, QT, and QTc (B and F) interval (corrected ECG QT Interval using the Bazett's or Fridericia's correction), heart rate, and overall interpretation, with recording of any abnormal findings. Ten- second rhythm strips will accompany each ECG. For the Screening visit, 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.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise and consistent ECG recordings. If a machine-read QTc value is prolonged, repeat measurements may not be necessary if a qualified physician's interpretation determines that the QTc values are in the acceptable range.

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

7.1.5. Clinical Laboratory Tests

Blood/urine samples for serum chemistry, coagulation, hematology, and urinalysis will be collected at Screening, and each clinic visit at Months 6, 12, 18, 24, 30, 36, 42, 48, 54, and 60 (End of Study visit) or Early Termination Visit. *Blood/urine samples will also be collected at Month 3 (Countries listed in Appendix 4.2).*

The following clinical laboratory parameters will be assessed:

Serum Chemistry		
Sodium	Alkaline Phosphatase	Retinol binding protein
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	Inorganic Phosphorus	Free T4
Alanine aminotransferase (ALT)	Aspartate aminotransferase (AST)	

Hematology		
Hemoglobin (Hgb)	White blood cell count	Lymphocytes
Hematocrit	Neutrophils	Monocytes
Red blood cell count	Lymphocytes	Eosinophils
Mean corpuscular volume	Platelets	Basophils
Mean corpuscular hemoglobin	Mean corpuscular hemoglobin concentration	

Cardiac Biomarkers	
NT-proBNP	Troponin I

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

Urinalysis	
pH	Blood (free Hgb)
Protein	Nitrite
Glucose	Urobilinogen
Ketones	Specific gravity
Bilirubin	Leukocyte esterase

Urinalysis will be a qualitative determination by dipstick at the site. If the urine dipstick demonstrates a positive blood, protein, nitrites or leukocyte esterase result, the specimen will be sent to the Central Laboratory for microscopic evaluation. In the event that a site is unable to perform a urine dipstick with all of the required tests, it is acceptable for the sample to be sent for urinalysis including a microscopic evaluation in place of a dipstick. This

testing can be performed at either the central or local laboratory. At minimum, this testing should include pH, protein, glucose, ketones, bilirubin, blood (free Hgb), nitrite, leukocyte esterase, urobilinogen, and specific gravity. If the testing returns an abnormal result, additional testing should be performed as deemed necessary according to the clinical judgment of the investigator.

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

7.2. Pregnancy Testing

For female subjects of childbearing potential, a urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed, before investigational product administration at the Screening visit, at every clinic visit, and at the End of Study or early termination visit. *A pregnancy test will also be performed at Month 3 (Countries listed in Appendix 4.2).* A negative pregnancy result is required before the subject may receive the investigational product. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected), and repeated at all study visits and at the end of the study to confirm the subject has not become pregnant during the study. Pregnancy tests may also be repeated as per request of institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product and from the study.

7.3. Contraception Check

For female subjects who, in the opinion of the investigator, are biologically capable of having children and are sexually active; at each telephone and clinic 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 case report form. Subjects will be instructed to continue use of birth control for at least 28 days after study participation. Subjects who have not followed contraception requirements as determined at the time of the post-study telephone call will be asked to confirm pregnancy status.

7.4. Other Assessments

7.4.1. New York Heart Association Classification

Subjects will be evaluated using the New York Heart Association (NYHA) classification (Appendix 3) at the Screening visit and at Month 6, 12, 18, 24, 30, 36, 42, 48, 54, 60 (or Early Study Discontinuation visit). *NYHA will also be evaluated at Month 3 (Countries listed in Appendix 4.2).*

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.

7.4.2. Kansas City Cardiomyopathy Questionnaire

The Kansas City Cardiomyopathy Questionnaire (KCCQ) (Green 2000)[3] 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 8 domains (Physical limitation, Symptom stability, Symptoms frequency, Symptom burden, Total symptom, Self efficacy, Social limitation, and Quality of life) and Clinical summary score, 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 Screening visit and at Months 6, 12, 18, 24, 30, 36, 42, 48, 54, and 60 (or Early Study Discontinuation) as listed in the Schedule of Activities. *Subjects will also complete KCCQ at Month 3 (Countries listed in Appendix 4.2).*

Study sites will be provided with an approved translated version of the KCCQ. The KCCQ can be found in Appendix 2.

7.4.3. Body Mass Index/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 the modified Body Mass Index (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).

7.4.4. 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.

7.4.5. Biopsy Documentation of Amyloid Deposition

For Cohort B only. 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 4.1.2], 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 ATTR-CM, analysis will be performed to confirm the precursor protein basis for amyloid deposition, by either: mass spectrometry, immunohistochemistry or scintigraphy [see Section 4.1.2].

7.4.6. TTR Genotyping

For Cohort B only: 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.

7.5. Banked Biospecimens

For Cohort B only: Banked biospecimens will be collected from subjects for exploratory research relating to the drug response. These collections are not typically associated with a planned assessment described in the protocol. They will be handled in a manner that protects each subject's privacy and confidentiality. Banked biospecimens will be assigned the subject's study identification code (ID) at the site. The data generated from these banked biospecimens will also be indexed by this ID. Biospecimens will be kept until destruction in facilities with access limited to authorized personnel, and biospecimen-derived data will be stored on password-protected computer systems. The key between the subject's ID and the subject's direct personally identifying information (eg, name, address) will be held at the study site. Biospecimens will be used only for the purposes described in the protocol and informed consent document; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored for many years (no time limit) to allow for research in the future, including research conducted during the lengthy drug-development process and also postmarketing research. Subjects may withdraw their consent for the use of their banked biospecimens at any time by making a request to the investigator; in this case, any remaining biospecimens will be destroyed, but data already generated from the biospecimens will continue to be available to protect the integrity of existing analyses.

Unless prohibited by local regulations or ethics committee decision, a 4-mL blood genomic banked biospecimen **Prep D1 (dipotassium edetic acid [ethylenediaminetetraacetic acid] [K_2EDTA] whole-blood collection optimized for DNA analysis)** will be collected at the time specified in the Schedule of Activities/Study Procedures section of the protocol to be retained for potential pharmacogenomic/genomic/biomarker analyses related to drug response. For example, 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 primary purpose is to examine DNA; however, the biospecimen may also be used to study other molecules (eg, RNA, proteins, and metabolites).

For countries listed in Appendix 6, additional banked biomarker samples (blood: Prep R1 optimized for RNA; Prep B1 optimized for plasma; urine: Prep M2) will be collected at Screening (Day 0) for potential research related to the disease under study. See Appendix 7 for details.

The banked biospecimens will be collected from subjects in unless prohibited by local regulations or IRB/EC decision. It is possible that the use of these biospecimens may result in commercially viable products. Subjects will be advised in the informed consent document that they will not be compensated in this event.

7.5.1. Additional Research

Unless prohibited by local regulations or IRB/EC decision, subjects will be asked to indicate on the consent form whether they will allow banked biospecimens to also be used to design and conduct research in order to gain a further understanding of other diseases and to advance science, including development of other medicines for patients.

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

7.6. Cardiac Biomarkers N-Terminal Pro-Hormone Brain Natriuretic Peptide (NT-proBNP) and Troponin I

After Protocol Amendment 4, blood sample for cardiac biomarkers (NT-proBNP and Troponin I) will be collected at Screening, and each clinic visit at Months 6, 12, 18, 24, 30, 36, 42, 48, 54, and 60 (End of Study visit) or Early Termination Visit. Specifications for sample collection can be found in the study laboratory manual. *NT-proBNP and Troponin I will also be collected at Month 3 (Countries listed in Appendix 4.2).*

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 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 a serious adverse event (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 nonserious AE 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 study.

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. SAEs 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 SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.

AEs (serious and non-serious) should be recorded on the case report form (CRF) from the time the subject has taken at least 1 dose of investigational product through the 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 may result, in this study, 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 CRF, which is a specific version of the 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 AE page and, if applicable, any associated AE(s) are captured on an 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:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- 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

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- 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.

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 section on Serious Adverse Event Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level 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 (× ULN) concurrent with a total bilirubin value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 × ULN or not available;

- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

  - For subjects with preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values and ≥3 × ULN, or ≥8 × ULN (whichever is smaller).

  Concurrent with

  - For subjects with preexisting values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 × ULN **or** if the value reaches ≥3 × 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 measurements 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 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 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 workup of persistent pretreatment laboratory 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;

- Preplanned 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 noninvasive 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 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 the 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 SAE 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 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 that 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 an SAE report form and an EDP 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 EDP supplemental 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 EDP 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 EDP supplemental 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 preprocedure 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 baby, 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:

- Spontaneous abortion includes miscarriage and missed abortion;

- 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 EDP 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 documents 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 AE.

An occupational exposure is reported to the 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 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 the Section on Subject Withdrawal)

Withdrawal due to AEs 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 or legally acceptable representative. In addition, each study subject or legally acceptable representative 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 time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EDP, 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 or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames 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. Nonserious 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

AE 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.

For Cohort A, analyses will be performed using tafamidis/tafamidis and placebo/tafamidis treatment groups. Subjects randomized to tafamidis in parent study B3461028 and continue on tafamidis in the extension study B3461045 will be grouped as tafamidis/tafamidis. Subjects randomized to placebo in study B3461028 and randomized to tafamidis in the extension study B3461045 will be grouped as placebo/tafamidis.

For Cohort B, since subjects in this cohort will all be administered the same dose, only overall descriptive statistics will be provided.

9.1. Sample Size Determination

There is no formal sample size calculation for this protocol. Subjects who meet enrollment criteria are eligible; up to 2000 subjects are expected to enroll in Protocol B3461045.

9.2. Analysis of Other Endpoints

9.2.1. Mortality (Cardiovascular-related)

For Cohort A, time to cardiovascular-related mortality will be calculated from the first dose of the randomized treatment (Study B3461028). Kaplan-Meier survival curves for each treatment group along with median survival times (if applicable) will be presented.

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 same manner as death. 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.

For Cohort B, time to cardiovascular related mortality will be calculated from the first dose of treatment. The Kaplan Meier survival curve along with median survival time (if applicable) will be presented.

9.2.2. Hospitalization

For Cohorts A and B, the frequency of hospitalizations (all-cause and cardiovascular-related) during the study will be summarized descriptively.

9.2.3. Kansas City Cardiomyopathy Questionnaire

For Cohort A, the Kansas City Cardiomyopathy Questionnaire (KCCQ, Appendix 2) will be summarized by the following summary scores calculated using the guidelines established in the KCCQ Scoring Instruction Manual:

Physical limitations	Self-efficacy
Symptom stability	Quality of life
Symptom frequency	Social limitation
Symptom burden	Overall summary score
Total symptom score	Clinical summary score

The overall and domain scores will be evaluated as a change from baseline at each visit using a MMRM with an unstructured covariance matrix (or as appropriate) with subjects as a random effect and treatment, visit, TTR genotype (variant and wild- type), and visit-by-treatment interaction, as fixed effects and baseline score as covariate. Data will also be summarized by each scheduled assessment.

For Cohort B, descriptive statistics will be provided.

9.2.4. New York Heart Association

For Cohorts A and B, subjects will be evaluated using the New York Heart Association (NYHA) classification (Appendix 3). Descriptive statistics will be presented by clinic visit for each classification: Class I, Class II, Class III, and Class IV (see Appendix 3 for definitions). The number and percentage of subjects who improved, worsened, or with no change from baseline will also be presented at each visit.

9.2.5. Body Mass Index/modified Body Mass Index

For Cohorts A and B, BMI and mBMI values at each visit and change from baseline will be presented in summary tables and data listings. Descriptive statistics will be provided by visit.

9.2.6. Cardiac Biomarkers NT-proBNP and Troponin I

For Cohorts A and B, descriptive statistics for change from baseline (initiation of tafamidis) in NT-proBNP and Troponin I concentration will be summarized.

9.3. Safety Analysis

The safety assessments in this study are listed in Section 7.1. The safety analysis population consists of all subjects who are enrolled in this study and who have taken at least one dose of study treatment. Except for all-cause mortality (Section 9.3.1), all safety endpoints in Section 9.3 will be analyzed descriptively for Cohorts A and B.

9.3.1. Mortality (All-cause)

For Cohort A, time to all-cause mortality will be calculated from the first dose of the randomized treatment (Study B3461028). Treated subjects from the parent study B3461028 who discontinue prior to the start of this study will also be included in this analysis.

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 and TTR genotype (variant and wild-type) as factors.

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 same manner as death. 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.

For Cohort B, time to all-cause mortality will be calculated from the first dose of treatment. The Kaplan Meier survival curve along with median survival time (if applicable) will be presented.

9.3.2. Adverse Events

All AE data collected on the CRF will be presented in summary tables and data listings.

All adverse events that are observed from the time of first dosing with study medication 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.

9.3.3. Physical Examinations and Vital Signs

Physical examinations and vital signs (lying and standing blood pressure and pulse, respiratory rate, and temperature) will be summarized using descriptive statistics.

9.3.4. Use of Concomitant Medications

All data on concomitant medication usage collected on the CRF will be presented in summary tables and in data listings.

9.3.5. Clinical Laboratory Tests

All clinical laboratory data (serum chemistry, coagulation, hematology, and urinalysis) will be subjected to clinical review and summarized by frequency of events and mean changes from baseline.

9.3.6. Electrocardiograms

ECG values at each visit and change from baseline will be presented in summary tables and data listings. Descriptive statistics will be provided for each test result by visit.

Centrally over-read ECG variables will be summarized by mean change from baseline to end of study 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 ≥450 msec, ≥480 msec, and ≥500 msec. Categories for QTcB and QTcF as change from baseline are: ≥30 msec increase, ≥60 msec increase, and ≥75 msec increase. QTcF is considered the primary QTc value as this correction is anticipated to be more appropriate.

9.4. Interim Analysis

Interim analyses may be performed if required to meet regulatory requirements and as requested by the Data Monitoring Committee. Interim analyses may also be performed during the course of the study to allow for the reporting of data to the scientific community.

9.5. 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 charter. The recommendations made by the E-DMC to alter the conduct of the study 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 that are not endpoints, to regulatory authorities, as appropriate.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct 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 study 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 study site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. 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 are true. Any corrections to entries made in the CRFs or 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 investigative 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, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to 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 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/Ethics Committee

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/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC 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 and 2008).

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 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 a numerical code based on a numbering system provided by Pfizer in order to de-identify study subjects. The study 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 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 must be reviewed and approved by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject (or his or her legally acceptable representative) is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a subject's legally acceptable representative, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his or her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse), and that the subject's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

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

12.4. Subject Recruitment

Subject recruitment efforts are not required for this study because this is an extension study.

12.5. 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 that 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 a sufficient number of 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/EC, or investigational product 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 studies 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 Pfizer-sponsored interventional studies conducted in patients 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.

EudraCT

Pfizer posts EU Basic 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.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients have 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.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the principal investigator of the results of the study based on information collected or generated by the principal investigator, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "Publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication. 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, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the 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 CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any Attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

16. REFERENCES

1. Almeida MR, Macedo B, Cardoso I, et al. Selective binding to transthyretin and tetramer stabilization in serum from patients with familial amyloidotic polyneuropathy by an iodinated diflunisal derivative. Biochem. J. 2004;381:351-56.

2. Gertz MA, Skinner M, Connors LH, et al. Selective binding of nifedipine to amyloid fibrils. Am J Cardiol. 1985;55 (13 Pt 1):1646.

3. Green CP, Porter CB, Bresnahan DR, et al. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiology 2000;35:1245-55.

4. Rapezzi C, et al. Transthyretin-related amyloidoses and the heart: a clinical overview. Nat Rev Cardiol 2010;7:398-408.

5. Rubinow A, Skinner M, and Cohen AS. Digoxin sensitivity in amyloid cardiomyopathy. Circulation 1981;63:1285-88.

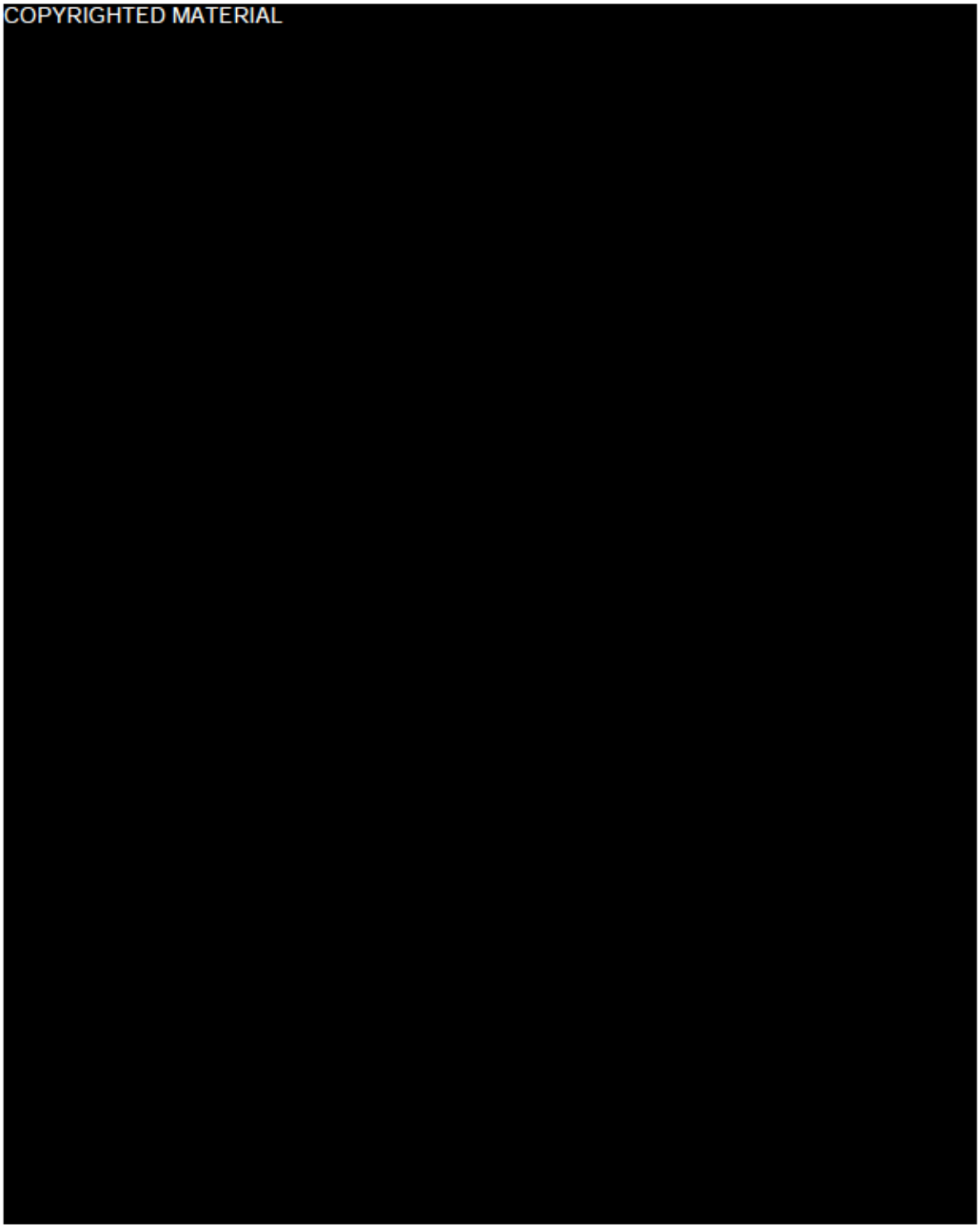
Appendix 1. Abbreviations

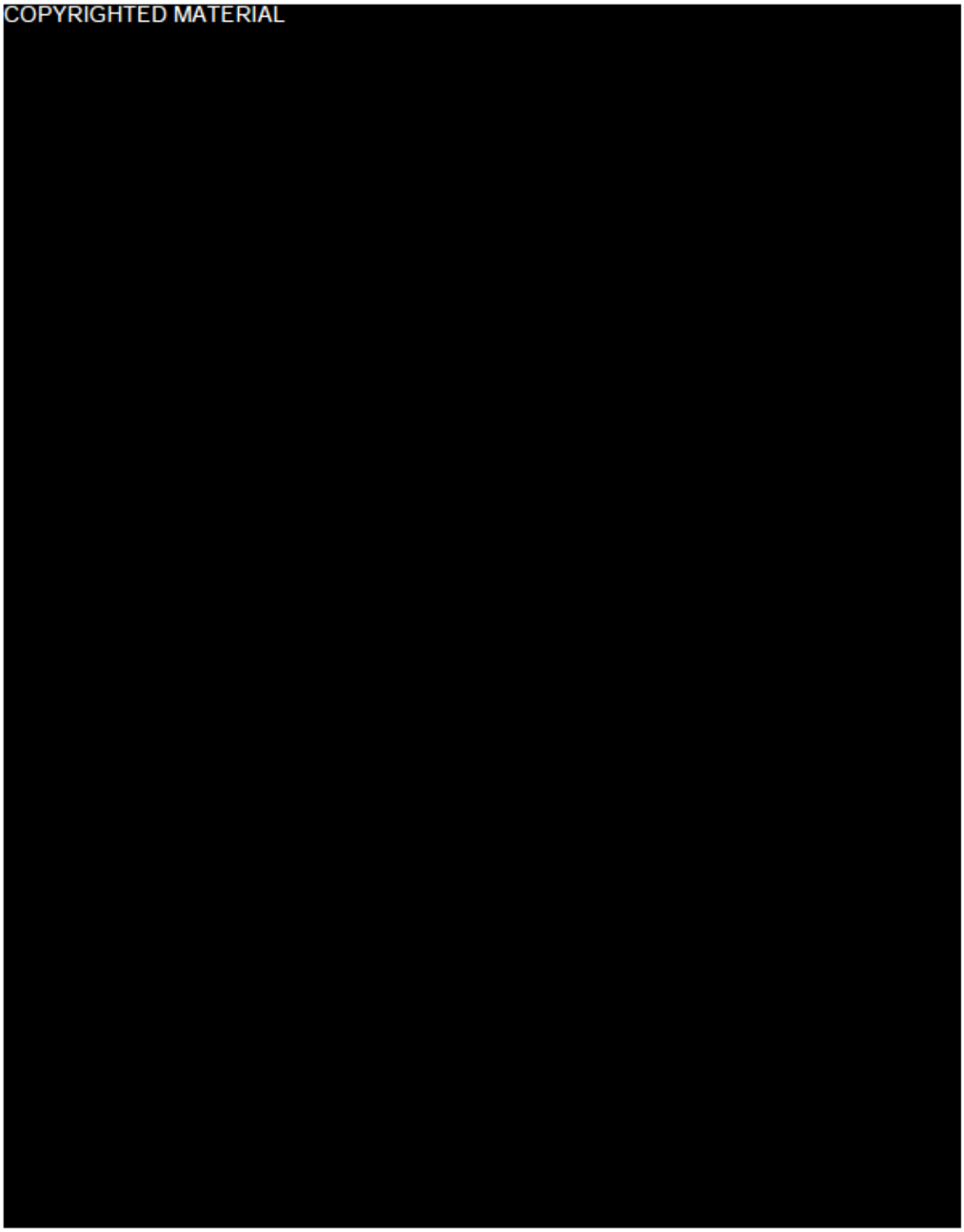
This is a list of abbreviations that may be used in the protocol.

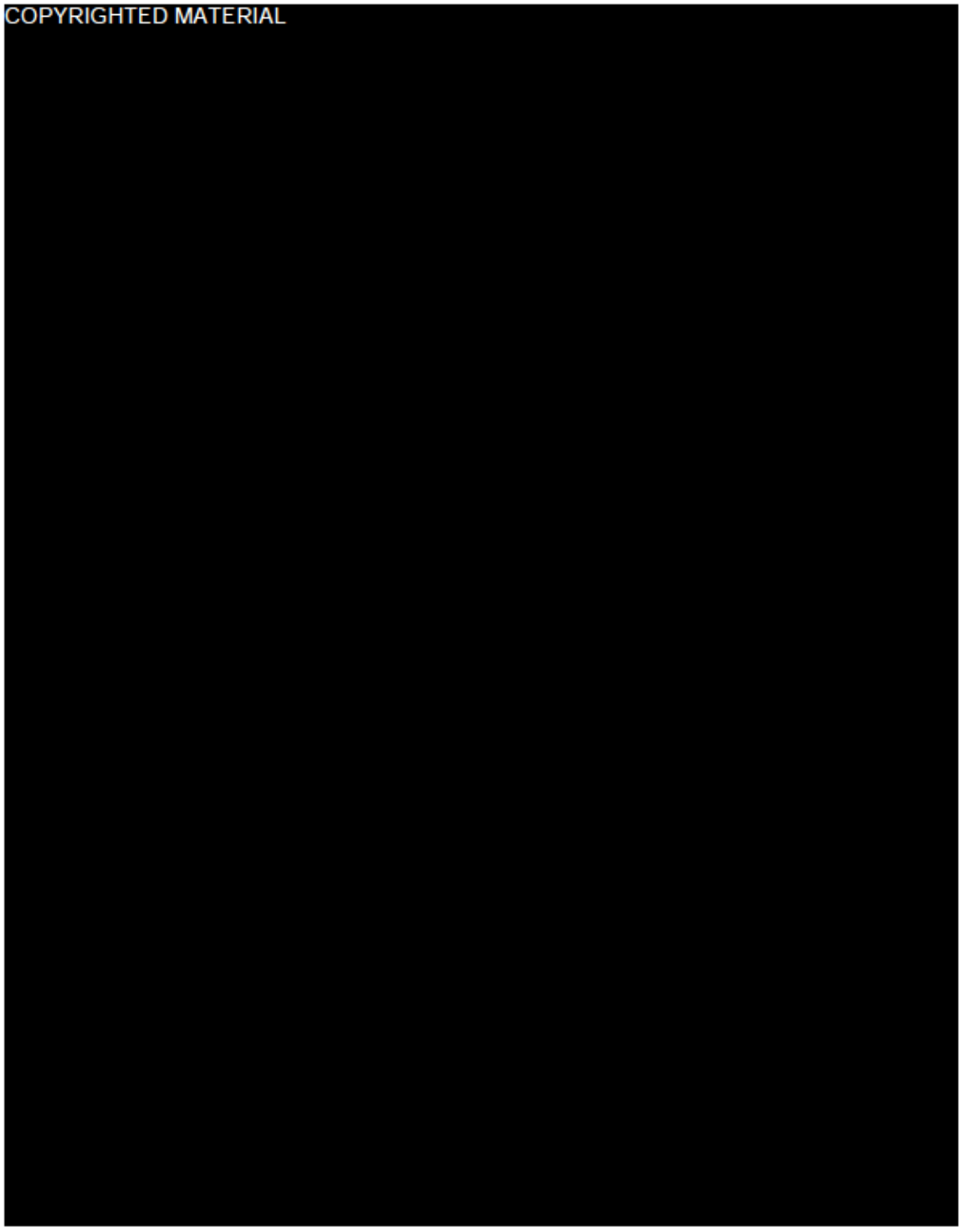
Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BBS	Biospecimen Banking System
BMI	Body Mass Index
CRF	case report form
CSA	clinical study agreement
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
DAI	dosage and administration instructions
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dispensable unit
EC	ethics committee
ECG	electrocardiogram
EDMC	external data monitoring committee
EDP	exposure during pregnancy
EDTA	edetic acid (ethylenediaminetetraacetic acid)
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HFpEF	heart failure with preserved ejection fraction
IB	investigator's brochure
ICD	informed consent document
ICH	International Conference on Harmonisation
ID	identification
IND	investigational new drug application
INR	international normalized ratio
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine system
IVR	interactive voice response
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
KCCQ	Kansas City Cardiomyopathy Questionnaire
LFT	liver function test
mBMI	Modified Body Mass Index

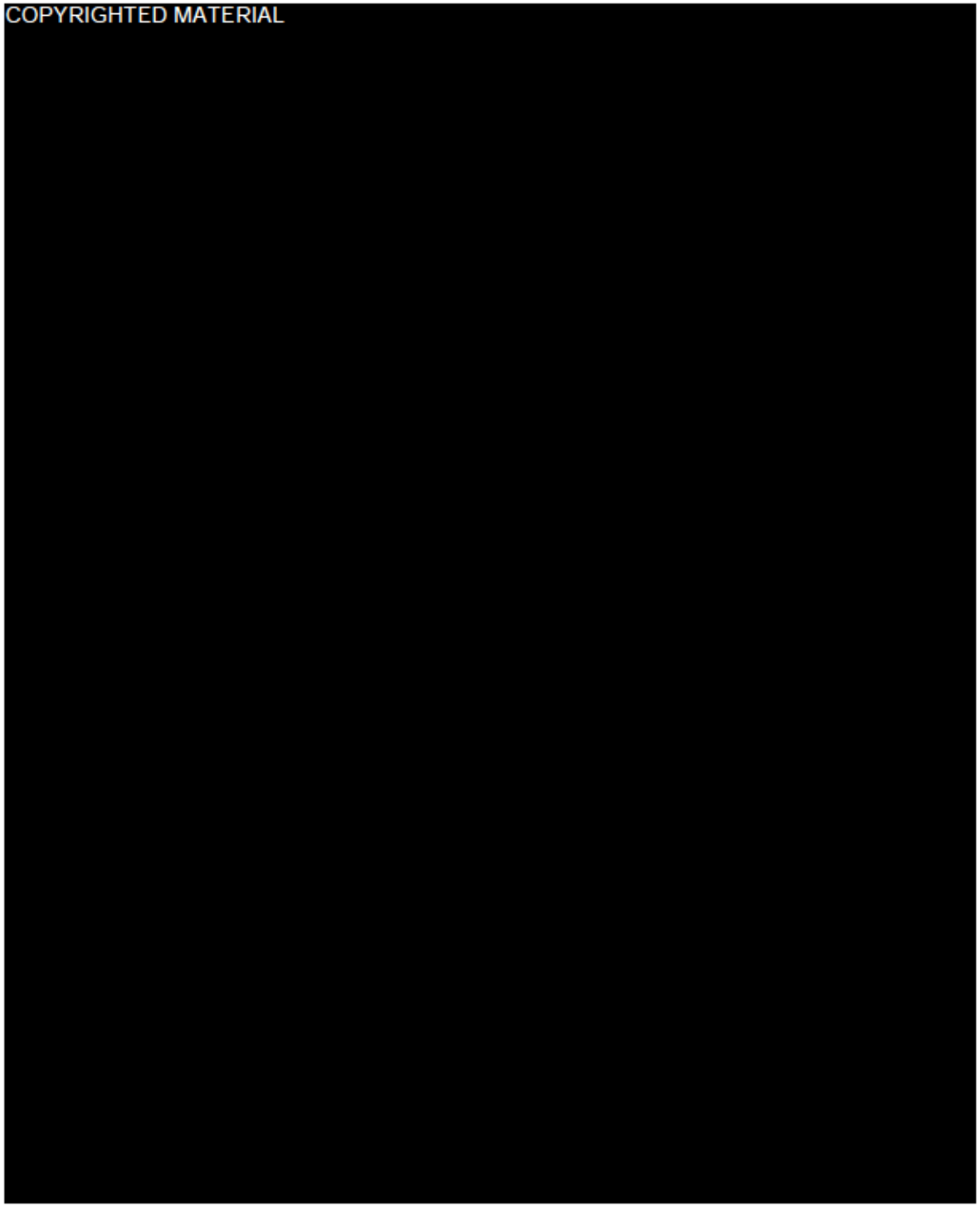
Abbreviation	Term
MGUS	Monoclonal gammopathy of undetermined significance
MR	Molar ratio
N/A	not applicable
NSAID	non-steroidal anti-inflammatory drug
NT-proBNP	N-terminal pro-hormone brain natriuretic peptide
NYHA	New York Heart Association
PT	prothrombin time
QTc (B and F)	Corrected ECG QT Interval using the Bazett's or Fridericia's correction
SAE	serious adverse event
SAP	statistical analysis plan
SIB	suicidal ideation and behavior
SOP	standard operating procedure
SPC	summary of product characteristics
SRSD	single reference safety document
SSID	study-specific identification number
TTR	transthyretin
ATTR-PN	transthyretin polyneuropathy
TTR-CM or ATTR-CM	transthyretin cardiomyopathy
ULN	upper limit of normal
US	United States
USPI	United States package insert
WOCBP	Woman of Child Bearing Potential

Appendix 2. Kansas City Cardiomyopathy Questionnaire

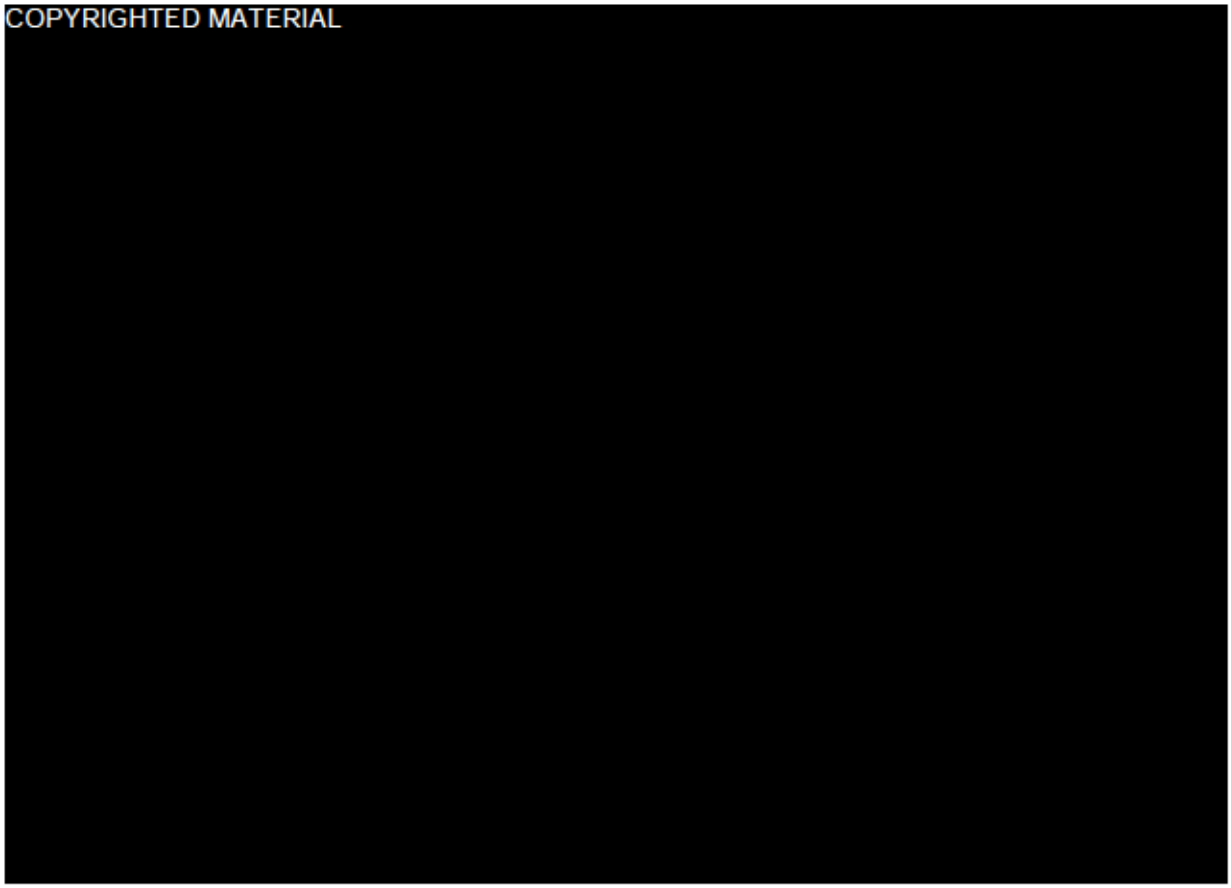








Appendix 3. New York Heart Association Classification



Adopted from: Dolgin M, editor. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. The Criteria Committee of the New York Heart Association. 9th ed. Boston: Little Brown & Co, 1994:253–256.

Appendix 4. Country-specific Protocol Requirements

Appendix 4.1. Study Duration

France and Germany only: The B3461045 study will end 24 months after the initial protocol approval date by the local Competent Authority. Continuation after the initial protocol approval period will depend on review of the final Clinical Study Report for parent study B3461028 by the local Competent Authority.

Appendix 4.2. Study Procedures

France and Germany only: Subjects are required to return to the study site for additional procedures at Month 3.

Japan only: Per local custom, study sites to contact all enrolled subjects by telephone at 2 weeks (±1 week) and 1 month (±1 week) after initiation of tafamidis 61 mg to check for adverse events/monitor safety.

Appendix 4.3. France Contrat Unique

This information relates to requirements for GCP Training, Investigational Product, and Inspections in France. The following supplementary text should be read in conjunction with this protocol:

- GCP Training: Prior to enrollment of any subjects, the investigator and any sub-investigators will complete the Pfizer-provided Good Clinical Practice training course ("Pfizer GCP Training") or training deemed equivalent by Pfizer. Any investigators who later join the Study will complete the Pfizer GCP Training or equivalent before performing Study-related duties. For studies of applicable duration, the investigator and sub-investigators will complete Pfizer GCP Training or equivalent every three years during the term of the Study, or more often if there are significant changes to the ICH GCP guidelines or course materials.

- Investigational Product: No subjects or third-party payers will be charged for investigational product.

- Inspections: The investigator(s) will notify Pfizer or its service provider immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its service provider to prepare the study site for the inspection and will allow Pfizer or its service provider (if not prohibited by law) to be present during the inspection. The study 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 service provider. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its service provider with an opportunity to review and comment on responses to any such findings.

Appendix 5. Countries Participating in Cohort B

Only study sites in the following countries may screen/enroll subjects in Cohort B:

- Australia;
- Argentina;
- Belgium;
- Canada;
- Czech Republic;
- France;
- Hong Kong;
- Japan;
- Netherlands;
- Spain;
- Sweden;
- Taiwan;
- United States.

Appendix 6. Countries that will Participate in Appendix 7 for Newly Enrolling Subjects

Only study sites in countries listed below may participate in the serum, plasma, and urine biomarker sample collection detailed in Appendix 7.

- Australia;
- France;
- Spain.

Appendix 7. Additional Sample and Banked Biospecimen Collection for Newly Enrolled Subjects in Countries Listed in Appendix 6

Objectives:

- Collection of blood and urine samples to support identification and characterization of biomarkers of transthyretin amyloidosis.
- Collection of additional banked biomarker samples to support exploratory research relating to drug response and other diseases.

Visit Identifier	Screening		
Population	Cohort B (without disease documentation)		Cohort B (with disease documentation)
Visit Window	Day -30	Day 0	Day 0
Informed Consent for Country-specific Sample and Banked Biospecimen Collection		X	X
Country-specific Sample and Banked Biospecimen Collection			
Collect blood for biomarkers and banked biospecimens[a]		X	X
Collect urine for biomarkers and banked biospecimens[a]		X	X
Record end-Diastolic interventricular septal wall thickness (mm)[a,b]		X	X
Record left ventricular posterior wall thickness (mm)[a,b]		X	X
Record left ventricular ejection fraction (%)[a,b]		X	X

a. Only for newly enrolling subjects in countries listed in Appendix 6.

b. Collect this data from medical history only if an echocardiograph performed in last 12 months prior to enrollment is available. This may be omitted if unavailable. Data can be entered at a subsequent study visit.

At the Screening visit (Day 0), blood and urine samples will be collected from newly enrolled subjects in the countries identified in Appendix 6. These subjects will have confirmed diagnosis of ATTR-CM but have never taken tafamidis. These samples will be used to support identification and characterization of serum, plasma, or urinary biomarkers of transthyretin amyloidosis. Results of these analyses will be reported elsewhere.

Identified biomarkers will be further characterized and validated using samples from other studies in patients with heart failure with preserved ejection fraction (HFpEF), or imaging evidence consistent with or suggestive of HFpEF or ATTR-CM who have been comprehensively evaluated for ATTR-CM.

At the Screening visit (Day 0) the following procedures will be conducted:

- Additional Informed consent for sample collection.

- Collect blood and urine samples for the following:
  - ATTR biomarker identification:
    - 45 mL blood (7.5 mL in each of 6 tubes) including 2 K_2-EDTA plasma samples, 2 lithium heparin plasma samples, and 2 serum sample tubes;
    - 10 mL urine.
  - Banked Biospecimens:
    - 2.5 mL whole blood Prep R1 optimized for RNA;
    - 10 mL whole blood Prep B1 optimized for plasma;
    - 10 mL urine (Prep M2).
- Collect the following echocardiography parameters from patient medical records from the previous 12 months prior to enrollment, if available. Only the most recent echocardiograph should be used if there are multiple results from the previous 12 months.
  - End-Diastolic interventricular septal wall thickness (mm);
  - Left ventricular posterior wall thickness (mm);
  - Left ventricular ejection fraction (%).

Banked Biospecimens will be collected as local regulations and IRBs/ECs allow.

Banked Biospecimens may be used for exploratory research relating to the drug response, the disease under study and other diseases as described in Sections 7.5 and 7.5.1. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the banked samples.

Detailed instructions on collection, processing, storage, shipment and contact information will be provided to the investigator site in the study laboratory manual.