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OPEN-LABEL SAFETY AND EFFICACY EVALUATION OF FX-1006A IN PATIENTS WITH V122I OR WILD-TYPE TRANSTHYRETIN (TTR) AMYLOID CARDIOMYOPATHY

Compound:	Fx-1006A/PF-06291826
Compound Name (if applicable):	tafamidis
US IND Number (if applicable):	[redacted]
Protocol Number:	Fx1B-303/B3461026
Phase:	3

[redacted]

The name, title, address and telephone number(s) of the sponsor's medical expert for the trial is documented in the study contact list located in the coordinator's manual.

Document History

Document	Version Date	Summary of Changes
Amendment 1	14 June 2012	1) Protocol - Update of sponsor name: FoldRx Pharmaceuticals, Inc is now a wholly-owned subsidiary of Pfizer, Inc. 2) Protocol – change in nomenclature for abbreviation from ATTR-CM and ATTR-PN to TTR-CM and TTR-FAP. 3) Protocol - extension of study duration to up to 10 years or until subject has access to tafamidis for TTR-CM via prescription. Upon regulatory approval for the treatment of TTR-CM in their respective country and access to prescription tafamidis, subjects may be withdrawn from the study. The decision to withdraw subjects in a country will be done in consultation between the investigator and the sponsor. 4) Protocol – change of term “patient” to “subject”. 5) Protocol number – changed from Fx1B-303 to Fx1B-303/B3461026. 6) Protocol - Update of drug name: The compound “Fx-1006A” (research number) is “tafamidis meglumine” (20 mg soft gelatin capsule), thereafter referred to as simply, “tafamidis”. 7) Protocol - Change in chemical compound name: [N-methyl D-(2,3,4,5,6-pentahydroxy-hexyl)-ammonium; 2-(3,5-dichloro-phenyl)-benzoxazole-6-carboxylate]. Changed to: [d-glucitol, 1-deoxy-1-(methylamino)-, 2-(3,5-dichlorophenyl)-6-benzoxazolecarboxylate (1:1)].

8) Renumbering of sections to align with standard Pfizer protocols:

Original section number	New section number
3.1	1.2
3.2	1.2.1
3.3	1.2.3
3.4	1.2.4
3.5	1.2.2
4	2.1
5.1	3 and 6
5.2	3.1
5.3	3.2
6.2	4.1
6.3	4.2
6.4	6.3
7.1	5.2.1
7.2	5.2.2
7.3	5.1
7.4	5.2.3
7.5	Removed
7.6	5.2.1
7.7	5.3
7.8	5.2.4
8, 8.1, 8.2, 8.3	6.1
8.4	7.2
8.5	7.4
8.6	7.3
8.7	7.5
8.8	7.6
8.9	7.1
8.10	6.2.4
9	replaced
10 (10.1-10.8)	9 (9.1-9.2.8)
11	Replaced 12
12	Replaced 15

		9) Schedule of activities – addition of allowable window for study visits. 10) Section 1.1 Indication - Indication has been added. 11) Section 1 - Updated non-clinical and clinical summary information. 12) Section 1.2.3: Non-Clinical Experience - update of Clinical experience to reflect most current IB. 13) Section 1.2.4: Clinical Experience - update of Clinical experience to reflect most current IB. 14) Section 2.2: Endpoints - section added. 15) Section 3: Study design – abbreviated. 16) Section 4.1: Inclusion Criteria – Inclusion of evidence of a signed informed consent document added. 17) Section 4.2: Exclusion Criteria - Added exclusion: Pregnant females; breastfeeding females; females of childbearing potential. 18) Section 4.3.1: Contraception – added section to increase clarity. 19) Section 5.3 Drug Storage and Accountability - Updated storage conditions for investigational product. 20) Section 6: Study Procedures • Addition of possibility for alternative options for study visits added. • Sections 6.1, 6.2 added to increase clarity of required assessments and procedures to be performed at each telephone and clinic visit.

		21) Section 8: Adverse Event Reporting: Transfer of pharmacovigilance from ICON to Pfizer, Inc. Updated to include Pfizer requirements. 22) Section 9.6 Interim Analysis: Addition of interim analysis. 23) Sections 10, 11, 12, 13, 14, 15 – replace sections 11 and 12 from FoldRx protocol to reflect Pfizer requirements.
Original protocol	19 June 2009	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country Health Authorities, IRB/ERB, etc.

PROTOCOL SUMMARY

Indication:
Tafamidis is being developed for the treatment of transthyretin amyloidosis, specifically targeting TTR polyneuropathy and cardiomyopathy

Study Objectives:

- To obtain additional, long-term, open-label safety and efficacy data for tafamidis in patients with transthyretin amyloid cardiomyopathy (TTR-CM).
- To continue to provide the investigational product tafamidis to patients with TTR-CM who completed Protocol Fx1B-201.

Study Population:
Male and female patients with V122I or wild-type TTR-CM who have not undergone liver or heart transplantation and who completed Protocol Fx1B-201 (a Phase 2, open-label study to evaluate TTR stabilization, as well as the safety and tolerability of tafamidis). Up to 35 patients are anticipated.

Test Product, Dose, and Mode of Administration:
Tafamidis 20 mg soft gelatin capsule once daily (at the same time each day).

Duration of Treatment: Up to 10 years or until subject has access to tafamidis for TTR-CM via prescription. Upon regulatory approval for the treatment of TTR-CM in their respective country and access to prescription tafamidis, subjects may be withdrawn from the study. Such subjects are considered study completers. The decision to withdraw subjects to transition to commercial supply will be done in consultation between the investigator and the sponsor.

Clinical Endpoints:
Safety

- Incidence of treatment-emergent adverse events;
- Physical examinations;
- Use of concomitant medications;
- Electrocardiograms (ECGs);
- Clinical safety laboratory tests;
- Vital signs.

Efficacy

- Patient Global Assessment;
- New York Heart Association (NYHA) Classification;
- 6-Minute walk test;
- Kansas City Cardiomyopathy Questionnaire (KCCQ);

- Echocardiography;
- Troponin I, troponin T, and amino-terminal B-type natriuretic peptide (NT-pro-BNP);
- Mortality and hospitalization (all cause and cardiac-related).

Inclusion Criteria:

- Evidence of a personally signed and dated informed consent document indicating that the subject (or a legal representative) has been informed of all pertinent aspects of the study.
- Patient successfully completed Protocol Fx1B-201.
- If female, patient is post-menopausal. If male, female partner is post-menopausal; or if female partner is of childbearing potential, then the patient is willing to use an acceptable method of birth control for the duration of the study and for at least three months after the last dose of study medication.
- Patient is, in the opinion of the Investigator, willing and able to comply with the investigational product regimen and all other study requirements.

Exclusion Criteria:

- Patient did not successfully complete Protocol Fx1B-201.
- Chronic use of non-protocol approved non-steroidal anti-inflammatory drugs (NSAIDs), defined as greater than 3 to 4 times/month. The following NSAIDs are allowed: acetylsalicylic acid, etodolac, ibuprofen, indomethicin, ketoprofen, nabumetone, naproxen, nimesulide, piroxicam, and sulindac.
- Patient has a clinically significant medical condition that, in the opinion of the Investigator, would place the patient at an increased risk to participate in the study.
- Pregnant females; breastfeeding females; females of childbearing potential.
- Patient has received a liver or heart transplant.

Study Design:

This is a Phase 3, open-label study designed to obtain additional long-term safety and efficacy data in patients who successfully completed Protocol Fx1B-201. These patients will be treated, with once daily 20 mg oral tafamidis (soft gelatin capsule) for up to 10 years from the date of enrollment in Protocol Fx1B-303, or until subject has access to tafamidis for TTR-CM via prescription. Upon regulatory approval for the treatment of TTR-CM in their respective country and access to prescription tafamidis, subjects may be withdrawn from the study. The decision to withdraw subjects to transition to commercial supply will be done in consultation between the investigator and the sponsor.

Subjects who successfully complete Fx1B-201 will report to the clinical unit on Day 0 to sign the informed consent form and determine eligibility for Protocol Fx1B-303. In addition, on Day 0, subjects will have their entrance criteria reviewed, and medical

histories and demographic characteristics obtained. The physical examination (including weight and vital signs) and the relevant end of study clinical laboratory tests (alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, gamma glutamyl transferase, creatinine, total bilirubin, international normalized ratio, troponin I, troponin T, and amino-terminal B-type natriuretic peptide) from Protocol Fx1B-201 will be used for Protocol Fx1B-303. If more than 30 days has elapsed between the final study visit of Protocol Fx1B-201 and Day 0 of Protocol Fx1B-303, an abbreviated physical examination (including weight and vital signs) and clinical laboratory assessments must be performed on Day 0.

Eligible subjects will begin once-daily dosing with 20 mg tafamidis at home on Day 1 (i.e., first dose) and will return to the clinical unit for study visits every 6 months.

Adverse events (AEs) and concomitant medication use will be collected at each 6-month visit to the clinical unit. Blood draws for clinical safety laboratory tests and abbreviated physical examinations (including weight and vital signs) will also be performed at each 6-month clinic visit. ECGs will be performed every 12 months on an annual basis. A telephone call will be made at 3-month intervals between clinic visits to assess safety and use of concomitant medications.

For the evaluation of efficacy, the Patient Global Assessment, NYHA classification, KCCQ, 6-minute walk test, and efficacy-related clinical laboratory tests (serum levels of troponin T, troponin I, and NT-pro-BNP) will be determined every 6 months. In addition, echocardiograms will be performed every 12 months on an annual basis.

An end of study visit including all safety and efficacy assessments will occur upon subject completion of the study, premature withdrawal (for any reason), or in the event of program discontinuation by the Sponsor.

Statistical Methods:
Safety and efficacy data will be summarized using descriptive statistics. For continuous variables, the means, standard deviations, medians, and ranges will be presented; for categorical variables, counts and percentages (with 95% confidence intervals) will be presented. Safety and efficacy data will also be shown in individual subject listings.

The cumulative efficacy data (starting from Protocol Fx1B-201) as measured by the Patient Global Assessment, NYHA classification, KCCQ, 6-minute walk test, echocardiograms, and serum levels of troponin I, troponin T, and NT-pro-BNP will be presented.

The endpoints of mortality and hospitalization (all cause and cardiac-related) will be analyzed individually and as composite measures. A Kaplan-Meier plot of time to event from the baseline of Protocol Fx1B-201 will be generated, and the event rate and associated 95% confidence intervals will be presented at 1, 2, 3, and 4 year intervals since the start of the investigational drug. The baseline data from protocol Fx1B-201 will be used as baseline for the analyses. Interim analyses will be performed during the course of the study to allow for the reporting of safety and efficacy data from the ongoing study.

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to Study Procedures (Section 6) and Assessments (Section 7) for detailed information on each procedure and assessment required for compliance with the protocol.

Procedure/Evaluation	End of study visit from Fx1B-201 and/or Day 0 (baseline)	Open-label Investigational Product			End of Study Visit[a]
		Day 1	Telephone (every 3 months between clinic visits)	Clinic Visit (every 6 months)	
		±1 week	±1 week	±2 week	±2 week
Informed consent	X				
Inclusion/exclusion criteria	X				
Demographics	X				
Medical history	X				
Complete physical examination					X
Abbreviated physical examination	X[b]			X	
Blood/urine sample for laboratory testing[g]	X[h]			X	X
Enrollment	X				
First dose of tafamidis		X[d]			
Patient Global Assessment				X	X
NYHA Classification				X	X
KCCQ				X	X
6-Minute walk test				X	X
Echocardiogram				Annually[e]	X[f]
Electrocardiogram				Annually[e]	X[f]
Adverse events	X		X	X	X
Concomitant medication	X		X	X	X
Tafamidis compliance and accountability				X	
Dispense tafamidis[c]	X		X	X	

[a] An end of study visit will occur upon subject completion of study, subject withdrawal (for any reason), or study discontinuation by the Sponsor.

[b] The physical examination (including weight and vital signs) results from the end of study visit from Protocol Fx1B-201 will be used for Day 0 of Protocol Fx1B-303. If more than 30 days has elapsed, then a brief physical examination must be performed on Day 0.

[c] Subjects will be given a 3-month supply of investigational product on Day 0. Subjects will return to the clinical unit every 6 months and will receive a 3-month supply of investigational product. At 3-month intervals between clinic visits, 3-month supplies of investigational product will be mailed directly to subjects from the clinical site.

[d] Subjects will self-administer study medication at home beginning on Day 1.

[e] Echocardiograms and ECGs will be performed on an annual basis (every 12 months).

[f] Echocardiograms and ECGs will be performed only if the previous assessments occurred more than six months prior to the end of study visit.

[g] Laboratory tests listed in Section 7.3.

[h] Clinical laboratory test results from the end of study visit from Protocol Fx1B-201 will be used for Day 0 of Protocol Fx1B-303. If more than 30 days has elapsed, then clinical laboratory tests must be performed on Day 0.

TABLE OF CONTENTS

LIST OF TABLES

APPENDICES

ABBREVIATIONS

Abbreviation	Definition
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
Asp38Ala	aspartate replaced by alanine at position 38
AST	aspartate aminotransferase
ATTR	TTR amyloidosis
ATTR-CM	Transthyretin amyloid cardiomyopathy
ATTR-PN	Transthyretin amyloid polyneuropathy
AUC	area under the concentration-time curve
BUN	blood urea nitrogen
C	Celsius
cm	centimeter
C_{max}	maximum plasma concentration
CRF	case report form
dL	deciliter
DMC	Data Monitoring Committee
EC	Ethics Committee
GCP	good clinical practice
GGT	gamma glutamyl transferase
Gly47Ala	glycine replaced by alanine at position 47
ICH	International Conference on Harmonisation
Ile107Val	isoleucine replaced by valine at position 107
IND	investigational new drug
INR	international normalized ratio
IRB	Institutional Review Board
KCCQ	Kansas City Cardiomyopathy Questionnaire
kg	kilogram
Leu58His	leucine replaced by histidine at position 58
mg	milligram
mL	milliliter
MRI	magnetic resonance imaging
NIS	Neuropathy Impairment Score
NIS-LL	Neuropathy Impairment Score – Lower Limb
nM	nanomolar
NOAEL	no observable adverse effect level
Norfolk QOL-DN	Norfolk Quality of Life-Diabetic Neuropathy
NSAID	non-steroidal anti-inflammatory drug
NT-pro-BNP	Amino-terminal B-type natriuretic peptide
NYHA	New York Heart Association
PD	pharmacodynamic

Abbreviation	Definition
Phe64Leu	phenylalanine replaced by leucine at position 64
PK	pharmacokinetic
SAE	serious adverse event
Ser77Phe	serine replaced by phenylalanine at position 77
Ser77Tyr	serine replaced by tyrosine at position 77
Thr60Ala	threonine replaced by alanine at position 60
TRACS	Transthyretin Amyloidosis Cardiac Study
TTR	transthyretin
TTR-CM	Transthyretin Cardiomyopathy
TTR-FAP	Transthyretin Familial Polyneuropathy
V122I	valine replaced by isoleucine at position 122
V30M	valine replaced by methionine at position 30
Val122Ile	valine replaced by isoleucine at position 122

1. INTRODUCTION

1.1. Indication

Tafamidis is being developed for the treatment of transthyretin amyloidosis, specifically targeting ATTR polyneuropathy and cardiomyopathy. This protocol will be specific for the ATTR cardiomyopathy (TTR-CM) indication.

1.2. Background and Rationale

Transthyretin amyloidosis (ATTR) is a disease induced by accumulation of insoluble fibrillar protein as amyloid in the tissues in amounts sufficient to impair normal function. The major phenotypic presentations are a sensorimotor and autonomic neuropathy (ATTR with polyneuropathy, or TTR-FAP) and restrictive cardiomyopathy (ATTR with cardiomyopathy, or TTR-CM). Transthyretin, a 127-amino acid, 55 kDa protein, primarily synthesized in the liver, is a secreted protein present in the blood and cerebrospinal fluid and is a carrier of thyroxine and retinol-binding protein-retinol (vitamin A) complex [1, 2]. In its native state, TTR exists as a homotetramer with two C2 symmetric funnel-shaped thyroxine binding sites located at the central dimer-dimer interface [3, 4, 5].

Natural amino acid sequence (wild-type) TTR and mutated variants of TTR can be involved in amyloid disease. However, mutated TTR species are more prone to accelerated fibrillogenesis, the most important risk factor for TTR amyloidosis [1, 2]. There are more than 80 TTR point mutations that have been associated with TTR amyloidosis [6]. All disease-associated mutations characterized thus far destabilize the TTR tetramer and many influence the velocity of rate-limiting tetramer dissociation [7]. An amyloidogenic mutation or aging can lead to tetramer dissociation into an alternatively folded monomeric amyloidogenic intermediate. This intermediate self-assembles into profilaments, filaments, and, under certain conditions, amyloid fibrils [8, 9]. In fact, the rate determining step for TTR amyloid formation is tetramer dissociation [10].

Cardiac involvement in ATTR, also known as familial amyloid cardiomyopathy when associated with variant TTR, or senile systemic amyloidosis (SSA) when associated with wild-type TTR, is associated with amyloid fibril infiltration of the myocardium, leading to diastolic dysfunction progressing to restrictive cardiomyopathy and congestive heart failure [3]. ATTR-CM is a late-onset disease with symptoms typically occurring in patients over 60 years of age. Although there are approximately 24 mutations associated with specific cardiac involvement, one common mutation, V122I (substitution of isoleucine for valine at position 122), has been reported with high frequency (prevalence of 3.4% to 3.9% [2]) in African-Americans. In an autopsy series, African Americans older than 60 years of age were found to be at greater risk of TTR amyloid cardiac deposits compared with Caucasians or Hispanics (1.6% vs. 0.4 and 0.13 respectively) [11]. In addition, 23% of the African American patients with TTR cardiac amyloidosis with evaluable DNA samples were heterozygous with the V122I mutation. Finally, all patients found to be V122I heterozygous had evidence of TTR cardiac amyloid on autopsy. These data confirm the association of the V122I TTR mutation with TTR amyloid cardiomyopathy and suggest a high clinical penetrance [11].

A mutation in TTR is not a pre-requisite for developing ATTR-CM. In the elderly, wild-type (normal) TTR may become structurally unstable resulting in deposition of amyloid fibrils primarily in heart tissue and leading to diastolic dysfunction, restrictive cardiomyopathy, and congestive heart failure [4, 5, 6, 7]. The frequency of TTR amyloid deposition in cardiac ventricles reported from autopsy studies in patients >80 years of age range from 1.8% [12] to 16.5% [13], with a rate of clinical cardiac disease pre-mortem of 34% [13].

For both wild-type and variant ATTR-CM, TTR amyloid fibrils are deposited in the myocardial interstitium, causing an increase in ventricular wall thickness, inducing myocardial damage and affecting myocardial function. Clinical symptoms include dyspnea on exertion, shortness of breath, orthostatic hypotension, syncope, and atrial fibrillation. Electrocardiogram findings demonstrate low voltage [14], particularly in light of the markedly thickened ventricular walls (median wall thickness of 17 mm [14]) demonstrated by echocardiogram. Amino-terminal B-type natriuretic peptide (NT-Pro-BNP), a serum marker of cardiac wall stress, is elevated in this population [15].

Current treatment is symptomatic, with careful fluid management and management of arrhythmias the mainstay. Median survival is approximately 60 months [14, 15], with 42% of patients dying from a cardiac cause [16]. Combined heart and liver transplantation is a current treatment option, however limited organ availability and significant patient co-morbidity limit transplant as a treatment option.

The natural history of TTR-CM was studied in the Transthyretin Amyloidosis Cardiac Study (TRACS), in a cohort of patients followed longitudinally for 24 months. Using a variety of cardiovascular monitoring examinations (e.g., electrocardiograms [ECG], echocardiography, cardiac magnetic resonance imaging [MRI], exercise tolerance testing), the study evaluated how the disease affects patients over time. This information will be utilized in two ways: (1) to better define the natural course of the disease; and (2) more importantly, to better understand how to measure the effectiveness of future treatments by identifying endpoints that are well-correlated with disease progression/regression and to support the selection of endpoints to be used in clinical trials.

Data on 29 patients (mean age 74 years) have been analyzed (18 wild-type and 11 V122I). Most patients are male (92%) and are New York Heart Association (NYHA) Classification I or II with significant cardiac symptoms reported at baseline. After an average follow-up time of 16 months, 11 patients died and one patient underwent cardiac transplant, giving the proportion of death/cardiac death of 41%, and a death rate per patient month exposure of 0.03. In addition, 41% of the patients experienced a cardiac hospitalization at least once, and 55% of the patients died or had a cardiac hospitalization. Preliminary analysis of cardiac assessments demonstrate significantly elevated NT-Pro-BNP and troponin levels, abnormal functional status as assessed by the 6-minute walk test, and significant diastolic dysfunction and thickened ventricles as assessed by echocardiography and cardiac MRI.

1.2.1. Tafamidis for the Treatment of TTR

Pfizer Inc is currently investigating tafamidis for the treatment of TTR-CM. Tafamidis meglumine [d-glucitol, 1-deoxy-1-(methylamino)-, 2-(3,5-dichlorophenyl)-6-benzoxazolecarboxylate (1:1)] is the meglumine salt form of 2-(3,5-dichloro-phenyl)-benzoxazole-6-carboxylic acid and is a novel, small molecule stabilizer of transthyretin. Specifically, tafamidis exhibits negative cooperative binding (i.e., dissociation constants of 2 nM [K_{d1}] and 154 nM [K_{d2}], respectively) to the two thyroxine binding sites on the native tetrameric form of TTR and thereby prevents its dissociation into monomers. At low pH, fibril formation of wild-type TTR and the most prevalent amyloidogenic variants, V30M and V122I, is potently inhibited by tafamidis. No fibril formation is observed for wild-type, V30M, and V122I variants at a 2:1 tafamidis:TTR stoichiometry. Under urea denaturating conditions, only 33% of TTR tetramer dissociates after incubation for 72 hours with equimolar quantity of tafamidis, when negligible tetramer dissociation is observed at a 2:1 tafamidis:TTR stoichiometry. Based on these data, it appears that a 1:1 tafamidis:TTR stoichiometry should be sufficient to stabilize TTR. The normal range of TTR level is between 18 and 38 mg/dL, corresponding to 3.2 to 6.8 μM of TTR. Therefore, plasma levels of 3.6 to 7.2 μM (~1-2 μg/mL) of tafamidis should stabilize TTR levels at least to the upper limit of the normal range.

In vitro addition of tafamidis to human plasma stabilizes wild-type, V30M, and V122I tetrameric TTR under strong urea denaturing conditions for at least four days. Under these same conditions most of the TTR is denatured in two days in the absence of stabilizer. Stabilization is observed at tafamidis concentrations between 3.6 and 7.2 μM for TTR plasma levels ranging from low (15.5 mg/dL [2.8 μM]) to high (28 mg/dL [5 μM]), confirming the effective therapeutic plasma level range between 3.6 and 7.2 μM (corresponding to ~1-2 μg/mL concentration of tafamidis in plasma). Ex-vivo results with plasma samples from initial Phase 1 clinical testing confirm this hypothesis and indicate that drug plasma levels between 0.7 to 1.7 μg/mL stabilize plasma TTR (when TTR plasma levels are between 16 and 36 mg/dL) after once a day dosing with tafamidis. Based on Phase 1 results, this drug level range would be achieved at steady-state after once-daily 20 mg (soft gelatin capsule), the tafamidis dose chosen for clinical evaluation.

1.2.2. Study Rationale

The initial development activities for tafamidis were undertaken in patients with TTR-FAP. Safety data in this population, and the results from the TRACS study, led to the initiation of Protocol Fx1B-201, a 12-month trial of tafamidis in patients with TTR-CM. The results of the Fx1B-201 study will be used in the design of a Phase 3 program that will evaluate the efficacy and safety of tafamidis in TTR-CM.

TTR-CM is a slowly progressing disease with a median survival of approximately 60 months [14, 15]. It is currently not known whether tafamidis will be effective in slowing or halting the progression of TTR amyloid cardiomyopathy, or when such an impact would become evident. Therefore, the purpose of the current study is to assess the long-term safety and

efficacy of tafamidis in patients with ATTR-CM. Eligible patients who successfully completed Protocol Fx1B-201, having received open-label tafamidis for 12 months, may enroll in Protocol Fx1B-303 and continue to receive open-label tafamidis for up to an additional 10 years.

1.2.3. Non-Clinical Experience with Tafamidis

Nonclinical pharmacology, pharmacokinetic (absorption, distribution, metabolism, and excretion; ADME), and toxicology studies conducted both in vitro and in vivo in the mouse, rat, rabbit, and dog have been completed. In vitro nonclinical studies have confirmed that the pharmacological activity of tafamidis is consistent with its high affinity binding to the two thyroxine binding sites of TTR in a non-cooperative manner and the resulting stabilization of TTR (wild type and amyloidogenic variants) by preventing dissociation of tetramers into monomers.

The general safety pharmacology profile of tafamidis demonstrated minimal nonselective binding to enzymes or ion channels, with no potential for anti-inflammatory activity. Tafamidis had minimal effects on either the central nervous system or cardiopulmonary physiology parameters in dogs. Tafamidis did not demonstrate the potential for QT prolongation. QTc shortening, observed at doses of 100 and 300 mg/kg, was associated with total plasma concentrations that exceeded 90 µg/mL. However, mean human steady-state maximum concentration ($C_{max)}$ values following the daily therapeutic dose of 20 mg in elderly and nonelderly subjects were 2.8 and 2.3 µg/mL respectively. Given the 30 to 40-fold difference in exposures, it is felt that the nonclinical observations have little relevance to the clinical profile of tafamidis.

Predictable pharmacokinetic behavior of tafamidis was demonstrated following oral administration in the nonclinical species. Tafamidis was absorbed following oral administration with an absolute bioavailability >90% and exhibited dose proportional increases in C_{max} and AUC at dose up to 30 mg/kg, but further increases in the administered dose provided less than proportional increases in systemic exposure, indicating saturation in the drug absorption. Terminal plasma half life is about 40 hours following a single administration. Drug accumulation has been confirmed in repeated dose studies.

Tafamidis is readily absorbed through the intestinal wall upon administration and is bound to a high extent to plasma proteins (>97%), essentially TTR and albumin. Tafamidis distributes widely in tissues (maternal and fetal), crosses the placental barrier to an extent of less than 5% of the initial dose, and ~ 30% of the dam's dose transferred into the milk.

Tafamidis demonstrated a high degree of metabolic stability and its limited biotransformation resulted in the formation of a monoglucuronide (acylglucuronide) as the primary metabolite in most of the nonclinical species and humans, while a monooxidative product was only detected in the mouse and rabbit. In rats, tafamidis is cleared primarily via biliary excretion and fecal elimination with some enterohepatic circulation, with a smaller contribution by the urine. A human ADME study suggests similar pathways are operative in humans.

Tafamidis meglumine has been evaluated in vitro to assess protein binding, induction and inhibition of cytochrome P450 enzymes (1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5), and inhibition of transporter protein P glycoprotein (P gp), with results suggesting very low likelihood for clinical drug-drug interactions. No significant CYP 450 inhibition was observed. A series of nonclinical toxicity studies were conducted in mice, rats, and dogs to assess the safety of tafamidis. The absence of acute toxicity following a single dose of tafamidis up to 600 mg/kg in dogs is indicative of a low risk for overdose. Tafamidis was well tolerated following repeated daily oral administration up to 26 weeks in rats and 39 weeks in dogs. The NOAEL was determined to be 30 mg/kg/day in the rat and 45 mg/kg/day in dog. When doses were increased above the NOAELs, rodents had a drug accumulation in their stomachs while dogs vomited. Other signs of toxicity accompanied these obvious signs, including decreased food intake, modified feces, stress related signs, increase in liver weight and in liver enzyme levels, lymphoid depletion, and kidney lesions in rodents.

Tafamidis was nongenotoxic in a battery of in vitro studies, although a slight increase in frequency of polyploid cells was observed at 100 and 200 µg/mL in the presence of S9 activation but not without metabolic activation in the in vitro chromosome aberration assay using human peripheral lymphocytes. Polyploidy is not considered to be a reliable surrogate marker for aneugenicity. The lack of risk for aneuploidy induction with tafamidis was further evidenced by the lack of micronucleus induction in the bone marrow of Sprague-Dawley rats at the doses producing C_{max} and AUC values significantly exceeding the predicted clinical exposures (~ 72X over the C_{max} and ~ 67X over the steady state $AUC_{(0-24)}$ observed in humans, based on exposure in a 4-week rat study). The evaluation of the carcinogenic potential in hemizygous Tg.rasH2 mice did not demonstrate an increase in the incidence of neoplasia.

Tafamidis did not demonstrate any effects on fertility, general reproductive performance and early embryo-fetal development in the rat and the maternal and paternal NOEL for reproductive toxicity was determined to be greater than 30 mg/kg/day. Developmental toxicity was evident in the rat by reduced fetal weights in the 30 and 45 mg/kg/day maternal dosage groups (developmental NOAEL = 15 mg/kg). Developmental toxicity in the rabbit was demonstrated by increased post-implantation loss, reduced fetal body weight and associated skeletal variations, and malformation at 8 mg/kg and skeletal variations at 2 mg/kg/day. The NOEL for developmental toxicity in rabbits was 0.5 mg/kg/day. Tafamidis-related toxicity in the developmental and perinatal/postnatal reproduction toxicity study in rats resulted in a NOAEL for reproductive toxicity and for viability and growth of the F1 generation of 5 mg/kg/day. Women of child-bearing potential should take measures to prevent pregnancy while being treated with tafamidis.

Non-clinical data indicate that there is a large safety margin above the anticipated human efficacious plasma concentration and those concentrations associated with toxicity in rats or dogs. Emesis was the most common form of clinical intolerance in the dog. Owing to the dosing strategy, the immediate emetic activity led to apparent aspiration of gastric contents and/or drug, leading to moribundity and subsequent euthanasia. The gastric impaction and

subsequent delayed gastric emptying, presumably followed by circulatory distress, shock and multiorgan failure, in rats was caused by a supraclinical dosing regimen and is not a relevant risk to human subjects. While the exact mechanism(s) for the toxicities observed following the oral administration of tafamidis has not been elucidated, there is an ample therapeutic margin to permit safe exposure to humans and there was no toxicity identified that would preclude human use, such as undetectable lesions or irreversible damage.

No target organs of tafamidis-related toxicity were identified in the repeated dose toxicity studies conducted in rats or dogs (26 weeks and 39 weeks, respectively). However, in the CByB6F1 hybrid mouse and the tg.rasH2 mouse, the liver and/or kidney have been identified as target organs as non-neoplastic lesions were noted following treatment for 28 days (CByB6F1 hybrid mouse) or 26 weeks (tg.rasH2 mouse). Nephrosis was the primary lesion noted in the kidneys, only in male mice and in a dose-dependent manner. In the liver, centrilobular hypertrophy and scattered single cell necrosis were present in male mice more than in the female mice in terms of the incidence of both lesions and the severity of the centrilobular hypertrophy. The incidence of both liver lesions was dose dependent. However, the mouse (CByB6F1) did not demonstrate a unique monooxide metabolite that was not present in the rat or dog, nor has it been detected in the plasma of humans administered tafamidis. However, a causal relationship between the monoxide metabolite and the liver and/or kidney lesions has not been established.

Generally, there were no significant toxicities observed in the repeated dose toxicology studies in the rat and dog. Therefore, tafamidis was considered to be well tolerated in the rat at dose levels up to 30 mg/kg/day for 26 weeks, providing an exposure ratio of 45- to 63-fold based on the human AUC at steady state, and in the dog at dose levels up to 45 mg/kg/day for 39 weeks providing an exposure ratio of 29- to 36-fold based on the human AUC at steady state. Additionally, there was no evidence for an increased risk of neoplasia at exposures at least 31-fold the human AUC nor was there evidence of any tafamidis-related genotoxicity. With the exception of the reproductive developmental toxicity findings, tafamidis has an excellent nonclinical safety profile.

Refer to the Tafamidis Investigator Brochure for further details.

1.2.4. Tafamidis Clinical Experience

The clinical development program for tafamidis has included 13 controlled and uncontrolled clinical trials and two non-interventional, observational studies completed primarily in patients with TTR-FAP. As of 13 May 2011, patients with TTR-FAP (n=127) received 20 mg of tafamidis administered daily for an average of 538 days (range of 15 to 994 days) or approximately 187 patient-years. The mean duration of exposure was 17.7 months: 87 were treated for at least 1 year, 43 were treated for at least 2 years, and 31 were treated for at least 30-<36 months.

The tafamidis 20 mg soft gelatin capsule (as used in the clinical studies) demonstrated a half-life average of 59 hours and $C_{avg(SS)}$ average of 2.07 µg/mL (SD=0.20). The tafamidis 20-mg soft gelatin capsule daily dose resulted in an average fluctuation (peak to trough) of

51.8%, with an average minimum concentration (C_{min}) of 1.61 µg/mL and an average C_{max} of 2.66 µg/mL. The average range was consistent with the 1 to 2 µg/mL required to stabilize TTR levels beyond the upper limit of the normal range; steady state was attained within 12 days, and exposure was consistent across subjects, with low variability across subjects for key PK parameters. Note that steady-state exposure was similar between males and females. Therefore, the 20 mg daily dose has been used in the development program. Further, based on a population PK analysis, no dose adjustment is necessary for the elderly or patients with hepatic or renal impairment.

The primary purpose of a therapy such as tafamidis is to stabilize the TTR tetramer, thus inhibiting the amyloid cascade and ultimately halting or slowing TTR-FAP disease progression over a sustained period of time. During the 18-month period of intervention in Study Fx-005, tafamidis slowed the course of neurological impairment and maintained quality of life in treated patients. Together, with the extension Study Fx-006 data, tafamidis demonstrated a sustained effect over 30 months, a period of time representing approximately 25% of the average TTR-FAPPN disease duration of 10 years. Further, Study Fx1A-201 was a small Phase 2II open label, single-treatment arm study designed primarily to determine the efficacy of tafamidis in stabilizing TTR variants other than the V30M (valine replaced by methionine at position 30) mutation. The results from this study of non-V30M TTR-FAP patients, which represented an older, more severely affected patient population, strongly supported the observed efficacy of tafamidis in V30M patients. As in Study Fx-005, the consistency of response across endpoints measuring different aspects of this multi-faceted disease was again observed following 12 months treatment with tafamidis. The results indicated the disease-modifying utility of tafamidis in treating all patients with TTR-FAPPN, regardless of mutation.

Study Fx1B-201 was a small Phase 2 study in TTR-CM in which a total of 35 patients were enrolled and analyzed, 31 patients with wild-type genotype and 4 with V122I genotype. As expected, the patients were elderly (mean age approximately 76 years), with significant disease duration (approximately 8 years) and signs and symptoms of mild to moderate cardiac dysfunction (84% with NYHA Class I or II) at the time of enrollment.

Tafamidis effectively stabilized TTR in 34 of 35 (97.1%) patients, representing both wild-type and V122I, at Week 6, with approximately 88% stabilized throughout the 12 months.

Following 12 months treatment with tafamidis, along with routine standard of care, 2/35 (5.7%) patients died, 9/35 (25.7%) experienced at least one cardiovascular hospitalization, and 9/35 (25.7%) experienced the composite endpoint of death or cardiovascular hospitalization. Results were similar between the TTR genotype groups. These data were numerically better than that reported in the TRACS historical control cohort, during which the 12-month rate of death, cardiovascular hospitalizations and death/cardiovascular hospitalizations were 6/29 (20.7%), 10/29 (34.5%) and 13/29 (44.8%), respectively.

Cardiac biomarkers (NT-proBNP, troponin I and T) at baseline were elevated, which was not unexpected given the patients' underlying cardiac involvement. The change in NT-proBNP over 12 months was relatively small, and numerically lower than that observed in TRACS. Troponin I and T, more specific markers of cardiac necrosis, remained stable, suggesting no substantial deterioration of cardiac status over 12 months of tafamidis treatment. These data are supported by the functional assessments of NYHA classification and 6MWT. At 12 months, 75% of the patients had improved or preserved NYHA classification, with the overall population demonstrating minimal change in distance walked (-11 meters). This maintained functional walking capacity is in contrast to the deterioration observed in TRACS at 12 months (-44 meters).

Non-invasive cardiac assessments demonstrated significant cardiac involvement at baseline, with substantial ventricular wall thickening (echocardiography and cardiac MRI) and elevated intra-cardiac filling pressures (echocardiography). There were no consistent clinically relevant changes in these parameters over time (echocardiography). For the wild-type patients (the majority of patients in the study), the deterioration in ejection fraction (-3.9) and stroke volume (-8.0) observed in the current study was less than that observed in TRACS (-10.5 and -15.4, respectively) at 12 months. Similar findings were observed in a subset of patients that underwent cardiac MRI. An additional finding in cardiac MRI was a decrease in percent of left ventricle (LV) mass with amyloid observed at 12 months in the small subgroup of patients undergoing this assessment, while there was an increase in LV mass with amyloid observed in TRACS.

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

Over the 12 months of tafamidis treatment, the patients' quality of life was maintained as was their functional status, as assessed by the SF-36, and KCCQ and PGA, respectively. The majority of these results were also better when compared with TRACS.

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

Overall, tafamidis was effective in achieving and maintaining TTR stabilization in both wild-type and V122I patients and showed an apparent stabilization of the progression of cardiac disease.

The safety data described reflect exposure of 127 TTR-FAP patients to 20 mg of tafamidis administered daily for an average of 538 days (ranging from 15 to 994 days). The population was composed of adult patients diagnosed with symptomatic TTR-FAP, with a mean age of approximately 44 years; approximately half of the patients were female, and approximately 90% of the patients were Caucasian. Note that primary evidence of safety and efficacy was obtained from a placebo-controlled 18-month study in patients with TTR-FAP.
Table 1 provides a summary of the most common treatment emergent adverse events (TEAEs) (≥5% in tafamidis treatment group) during study Study Fx-005.

Table 1. Summary of Most Common (≥5% in Tafamidis Treatment Group) Treatment-Emergent Adverse Events Sorted in Descending Incidence in the Overall Tafamidis Group – TTR-FAP Patients, Study Fx-005 (Safety Population)

	Number (%) of Subjects	
MedDRA Preferred Term	**Tafamidis 20 mg N=65**	**Placebo N=63**
Number of patients with at least 1 AE	60 (92.3)	61 (96.8)
Diarrhea	17 (26.2)	11 (17.5)
Urinary tract infection	15 (23.1)	8 (12.7)
Pain in extremity	11 (16.9)	6 (9.5)
Headache	10 (15.4)	12 (19.0)
Influenza	10 (15.4)	9 (14.3)
Nasopharyngitis	9 (13.8)	8 (12.7)
Upper abdominal pain	8 (12.3)	2 (3.2)
Nausea	8 (12.3)	8 (12.7)
Vomiting	7 (10.8)	8 (12.7)
Lacrimation decreased	6 (9.2)	7 (11.1)
Back pain	5 (7.7)	4 (6.3)
Myalgia	5 (7.7)	2 (3.2)
Punctate keratits	5 (7.7)	3 (4.8)
Anxiety	4 (6.2)	3 (4.8)
Constipation	4 (6.2)	7 (11.1)
Depression	4 (6.2)	3 (4.8)
Erectile dysfunction	4 (6.2)	4 (6.3)
Peripheral edema	4 (6.2)	8 (12.7)
Pharyngitis	4 (6.2)	5 (7.9)
Thermal burn	4 (6.2)	5 (7.9)
Upper respiratory tract infection	4 (6.2)	3 (4.8)
Vaginal infection	4 (6.2)	1 (1.6)

Adverse drug reactions (ADRs) were determined by including review of all treatment emergent adverse events, both serious and non-serious, regardless of investigator relatedness assessment, and review of vital sign data, laboratory data (including electrocardiogram data)

and discontinuations due to adverse events. In addition, other factors taken into consideration for the determination of ADRs included but were not limited to the mechanism of action of tafamidis, the known symptoms of the underlying TTR amyloidosis, the temporality of the adverse event to the administration of tafamidis, and the relative rates of comparative adverse events in the placebo groups in the controlled trials. Based on the review of the totality of the available safety data, it was determined that there are four adverse events for which there is basis to believe there is a causal relationship between their occurrence and the use of tafamidis; as such these adverse events were identified as ADRs, with the incidence observed in the placebo-controlled 18 month Phase 2/3 Study Fx-005 presented in Table 2.

Table 2. Summary of Adverse Drug Reactions

System Organ Class Preferred Term	Tafamidis N=65 n (%)	Placebo N=63 n (%)
Gastrointestinal disorders		
Diarrhea	17(26)	11(18)
Upper abdominal pain	8(12)	2(3)
Infections and infestations		
Urinary tract infection	15(23)	8(13)
Vaginal infection*	4(12)	1(3)

There were no meaningful changes in vital signs, clinical laboratory parameters, ECG parameters (including QTc interval), or other safety parameters measured. No meaningful changes in echocardiogram and ECG were observed for patients with a medical history of cardiomyopathy. Tafamidis has been well tolerated by both healthy subjects during the Phase 1 clinical studies as well as in patients during the Phase 2 and 3 clinical studies.

Tafamidis was also studied in patients with TTR cardiomyopathy in Study Fx1B-201. These patients were elderly (mean age 76 years) with signs and symptoms of mild to moderate cardiac dysfunction. While there was no placebo control group, the adverse event profile of tafamidis reported during this study reflects the patients' underlying disease, co-morbid conditions, and elderly status. The most frequent adverse events overall were related to the symptoms and episodes of heart failure (dyspnea, cardiac failure and edema). Eighteen (51.4%) patients reported at least one TEAE that was considered at least possibly related to study medication as assessed by the Investigator. The most common (>5%) treatment-related TEAEs included balance disorder (14.3%), ageusia (8.6%), constipation, diarrhea, edema peripheral, fall, weight increased, and decreased appetite and dyspnea (5.7% each). The majority (≥85%) of patients experienced TEAEs considered mild or moderate in severity. One event of hyperkalemia reported during a hospitalization for decompensated heart failure and associated with acute renal failure was considered life-threatening, and not related to tafamidis.

Complete information for this compound may be found in the Single Reference Safety Document, which for this study is the Investigators Brochure.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

- To obtain additional, long-term, open-label safety and efficacy data for tafamidis in subjects with TTR-CM.
- To continue to provide the investigational product tafamidis to subjects with TTR-CM who have completed Protocol Fx1B-201.

2.2. Endpoints

The efficacy endpoints for this study are:

- Patient Global Assessment;
- New York Heart Association (NYHA) Classification;
- 6-Minute walk test;
- Kansas City Cardiomyopathy Questionnaire (KCCQ);
- Echocardiography;
- Troponin I, troponin T, and amino-terminal B-type natriuretic peptide (NT-pro-BNP);
- Mortality and hospitalization (all cause and cardiac-related).

The safety endpoints for this study are:

- Incidence of treatment-emergent adverse events;
- Physical examinations;
- Use of concomitant medications;
- Electrocardiograms (ECGs);
- Clinical safety laboratory tests;
- Vital signs.

3. STUDY DESIGN

This is a Phase 3, open-label study designed to obtain additional, long-term, open-label safety and efficacy data for tafamidis, and to continue to provide subjects who have completed Protocol Fx1B-201 (a Phase 2, open-label study to evaluate TTR stabilization, as well as the safety and tolerability of tafamidis) with 20 mg oral tafamidis (soft gelatin capsule) for up to 10 years or until subject has access to tafamadis for TTR-CM via prescription. Upon regulatory approval for the treatment of TTR-CM in their respective country and access to prescription tafamadis, subjects may be withdrawn from the study. Such subjects will be considered study completers. The decision to withdraw subjects to transition to commercial tafamidis will be done in consultation between the investigator and the sponsor (see section 6.3).

Subjects who successfully complete Protocol Fx1B-201 will be eligible to enter study Fx1B-303.

3.1. Rationale for Study Design and Control Group

This is an open-label study designed to obtain additional safety and efficacy data and to continue to provide tafamidis to subjects with TTR-CM who have not had a liver or heart transplant and who have completed Protocol Fx1B-201. A control group will not be included in this open-label study design.

3.2. Study Duration and Dates

Enrolled subjects will receive 20 mg tafamidis (soft gelatin capsules) for up to 10 years or until subject has access to tafamadis for TTR-CM via prescription. Upon regulatory approval for the treatment of TTR-CM in their respective country and access to prescription tafamadis, subjects may be withdrawn from the study. The decision to withdraw subjects to transition to commercial tafamidis will be done in consultation between the investigator and the sponsor (see section 6.3).

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 protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

4.1. Inclusion Criteria

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

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

- Evidence of a personally signed and dated informed consent document indicating that the subject (or a legal representative) has been informed of all pertinent aspects of the study.

- Male or female subjects with TTR-CM who have not undergone liver or heart transplantation and who have successfully completed Protocol Fx1B-201.

- Subject has successfully completed Protocol Fx1B-201.

- If female, subject is post-menopausal. If male, female partner is post-menopausal; or if female partner is of childbearing potential, then the subject is willing to use an acceptable method of birth control for the duration of the study and for at least three months after the last dose of study medication.

  Note: The definition of acceptable method of birth control will be based on the judgement of the Investigator or designated associate.

4.2. Exclusion Criteria

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

1. Subject has not successfully completed Protocol Fx1B-201.

2. Chronic use of non-protocol approved non-steroidal anti-inflammatory drugs (NSAIDs), defined as greater than 3 to 4 times/month. The following NSAIDs are allowed: acetylsalicylic acid, etodolac, ibuprofen, indomethicin, ketoprofen, nabumetone, naproxen, nimesulide, piroxicam, and sulindac.

3. Subject has a clinically significant medical condition that, in the opinion of the Investigator, would place the subject at an increased risk to participate in the study.

4. Pregnant females; breastfeeding females; females of childbearing potential.

5. Subject has received a liver or heart transplant.

4.3. Life Style Guidelines

4.3.1. Contraception

All female subjects must be postmenopausal.

All male subjects with partners of childbearing potential 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 3 months after the last dose of investigational product. The

investigator, in consultation with the subject, will select the most appropriate method of contraception for the individual subject. The investigator, at each study visit, will confirm and document consistent and correct use. In addition, the investigator will instruct the subject to call immediately if the selected birth control method is discontinued or if pregnancy is known or suspected.

5. STUDY TREATMENTS

5.1. Allocation to Treatment

This is an open-label, single-treatment study. All enrolled subjects will be assigned to receive a single oral daily dose of 20 mg tafamidis.

5.2. Drug Supplies

5.2.1. Formulation and Packaging

Tafamidis [d-glucitol, 1-deoxy-1-(methylamino)-, 2-(3,5-dichlorophenyl)-6-benzoxazolecarboxylate (1:1)] is the meglumine salt of 2-(3,5-dichloro-phenyl)-benzoxazole-6-carboxylic acid. Tafamidis will be supplied by the Sponsor as opaque 12 oblong soft gelatin capsules filled with a suspension containing 20 mg of tafamidis.

Investigational product will be supplied in 10-count child resistant blisterpacks.

Study medication labels will contain: the kit number, tafamidis, dosage and strength, quantity of dosage units, route of administration, directions for use, protocol number, study sponsor, storage conditions, emergency contact information, and a caution statement regarding the investigational status of the compound.

5.2.2. Preparation and Dispensing

Investigational product will be dispensed to subjects according to the following schedule:

- On Day 0, an initial 3-month supply of investigational product will be dispensed to subjects at the clinical unit. Subjects will take their first dose of investigational product at home beginning on Day 1 (i.e., first dose).

- At 3-month intervals between clinic visits, 3-month supplies of investigational product may be mailed from the clinical site directly to subject's home.

- Every six months subjects will return to the clinical unit and will be instructed to bring all investigational product and packaging with them to determine investigational product compliance and accountability. At these clinic visits, 3-month supplies of investigational product will be dispensed directly to subjects for self-administration at home.

5.2.3. Administration

All enrolled subjects will self-administer a once-daily oral dose of 20 mg tafamidis at home as instructed by the clinical staff. All investigational product is to be taken by mouth, with water. Subjects will be instructed to take investigational product at the same time each day throughout the treatment period.

Medication errors may result, in this study, from the administration or consumption of the drug by the subject at the wrong time, or at the wrong dose strength. Such medication errors occurring to a study participant are to be captured on the adverse event (AE) page of the CRFs 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 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 and, if applicable, any associated adverse event(s) is captured on an adverse event (AE) CRF page (refer to Adverse Event Reporting section for further details).

5.2.4. Compliance

All investigational product will be self-administered by subjects at home. Subjects should be instructed to bring all investigational product and packaging to each follow-up visit to the clinical unit every six months. Compliance to investigational product will be determined through capsule counting procedures at subject visits to clinic. Compliance will be monitored and recorded in each subject's case report form (CRF). Additionally, investigational product accountability audits will be performed by the study monitor during routine monitoring visits.

5.3. Drug Storage and Drug Accountability

All investigational product (tafamidis) should be stored at controlled room temperature 15-25°C (59-77°F). Investigational product should be stored in its original package and should be protected from light.

Storage conditions stated in the Investigator Brochure (IB) may be superseded by the label storage.

Temperature of storage conditions should be monitored using validated devices that record maximum and minimum temperatures, are regularly calibrated, and data are regularly recorded. Should the product experience temperature excursion, relative to label instruction, during storage, then the impact to product quality and use should be addressed with relavant subject matter experts and documented accordingly.

Occasional short-term excursions from the intended storage conditions may occur. If the duration is short and the deviation in temperature is small, an investigation into the quality of the product is generally not required.

Subjects should be reminded of the storage conditions when drug is dispensed.

5.4. Concomitant Medication(s)

On Day 0, in conjunction with the review of their medical history, all subjects will be asked what medications they are taking. Thereafter, subjects will be asked what medications they have been taking at 3-month intervals (i.e., during clinic visits every 6 months and via telephone contact at 3-month intervals between clinic visits). All concomitant medications will be recorded on the CRF.

- Chronic use of non-protocol approved non-steroidal anti-inflammatory drugs (NSAIDs), defined as greater than 3 to 4 times/month is not permitted.

- The following NSAIDs are allowed: acetylsalicylic acid, etodolac, ibuprofen, indomethicin, ketoprofen, nabumetone, naproxen, nimesulide, piroxicam, and sulindac.

6. STUDY PROCEDURES

Every effort should be made to ensure that scheduled visits are made and protocol required tests and procedures are completed as described. From time to time there may be circumstances, outside of the control of the investigator, which may not make a clinic visit possible. In these cases, with prior discussion and approval from the sponsor, alternative options may be considered. Approved alternate options will not be considered protocol deviations.

Study procedures are outlined in the Schedule of Activities.

6.1. Screening/Baseline Assessment

The end of study physical examination (including weight and vital signs) and the relevant clinical laboratory assessments from Protocol Fx1B-201 will be used as the Day 0 assessments for Protocol Fx1B-303. If more than 30 days has elapsed between the final study visit of Protocol Fx1B-201 and Day 0 of Fx1B-303, an abbreviated physical examination (including weight and vital signs) and clinical laboratory assessments must be performed on Day 0.

Subjects will be required to sign an informed consent form before beginning participation in Protocol Fx1B-303. The following procedures will be performed on Day 0:

- All inclusion and exclusion criteria will be reviewed to ensure eligibility for participation in this study.
- Demographics (date of birth, age, gender, and race) for all subjects will be collected.
- A complete medical history will be obtained.
- Abbreviated physical exam including weight and vital signs (if not conducted within 30 days of Day 0).
- Collect blood/urine samples for clinical laboratory assessments (Section 7.3) (if not collected within 30 days of Day 0).
- Ask subjects non-leading questions such as "How do you feel?" and record adverse events.
- Record concomitant medications.
- Dispense 3 month supply of investigational product with instructions that subject is to administer the first dose at home on the following day as instructed (Section 5.2.3).

6.2. Study Period

6.2.1. Months 3, 9, 15, 21, 27, 33, 39, 45, 51, 57, 63, 69, 75, 81, 87, 93, 99, 105, 111, 117

Subjects will be contacted by telephone, contact is to be made ± 1 week of scheduled time:

- Ask subjects non-leading questions such as "How do you feel?" and document adverse events.
- Record concomitant medications.
- Mail 3 month supplies of investigational product following telephone contact.
- These phone visits can be conducted in person at the clinic at the discretion of the sites.

6.2.2. Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, 96, 102, 108, 114

Subjects will return to the clinic for the following assessments. Visits are to occur ± 2 weeks of the scheduled time:

- Conduct abbreviated physical examination, including weight and vital signs.

- Collect blood/urine samples for clinical laboratory assessments (section 7.3).
- Perform Patient Global Assessment.
- Determine NYHA Classification.
- Administer Kansas City Cardiomyopathy Questionnaire.
- Conduct 6-minute walk test.
- Ask subjects non-leading questions such as "How do you feel?" and record adverse events.
- Record concomitant medications.
- Determine drug compliance and accountability.
- Dispense 3 month supply of investigational product.

6.2.3. Months 12, 24, 36, 48, 60, 72, 84, 96, 108

In addition to the above assessments, collect ECG and echocardiogram every 12 months.

6.2.4. End of Study Visit

The end of study visit will occur upon subject withdrawal from the study or upon subject completion (up to 10 years or until subject has access to tafamadis for TTR-CM via prescription). Upon regulatory approval for the treatment of TTR-CM in their respective country and access to prescription tafamadis, subjects may be withdrawn from the study. Such subjects will be considered study completers. The decision to withdraw subjects in a country will be done in consultation between the investigator and the sponsor (see Section 6.3), subject withdrawal (for any reason), or program discontinuation by the Sponsor. The following activities will be completed:

- Complete physical examination, weight and vital signs.
- Collect blood samples for clinical laboratory assessments (section 7.3).
- Perform Patient Global Assessment.
- Determine NYHA Classification.
- Administer Kansas City Cardiomyopathy Questionnaire.
- Conduct 6-minute walk test.

- Echocardiogram (unless performed within 6 months prior).
- Electrocardiogram (unless performed within 6 months prior).
- Ask subjects non-leading questions such as "How do you feel?" and record adverse events.
- Record concomitant medications.
- Determine drug compliance and accountability.

In the event a subject is unable to return to the study site for the end of study visit, telephone contact with the subject approximately 30 days after the last dose of medication to assess adverse events and concomitant medications and treatments is expected. If laboratory assessments are needed to follow-up unresolved adverse events, retrieval of assessments performed at an institution local to the subject is acceptable.

The outcome of adverse events with a date of onset during the study period should be reevaluated, and any new adverse events should be recorded. All serious adverse events, and those non-serious adverse events assessed by the investigator as possibly related to study drug should continue to be followed even after subject withdrawal from study. These adverse events should be followed until they resolve or until the investigator assesses them to be "chronic" or "stable". Additional information on Adverse Event Reporting can be found in Section 8.

6.3. Subject Withdrawal

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. In addition, the Sponsor may choose to discontinue this study, at which time all subjects will be withdrawn.

A subject may be withdrawn from the study for any of the following reasons:

- Withdrawal of consent;
- Adverse event;
- Protocol noncompliance;
- Subject lost to follow-up;
- Subject death.

Subjects who are prematurely withdrawn from the study will not be replaced. Subjects who discontinue from the study at any time following enrollment will have a final end of study visit performed, including all safety and efficacy assessments, at the time of discontinuation.

Upon regulatory approval of tafamadis for the treatment of TTR-CM in their respective country, and access to prescription tafamidis, subjects may be withdrawn from the study. The decision to withdraw subjects in a country will be done in consultation between the investigator and the sponsor. Subjects will have all end of study procedures completed prior to study withdrawal. These subjects are considered completers.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the subject to return all unused investigational product(s), request the subject to return for a final visit, if applicable, 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. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

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 which he/she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.1. Efficacy Assessments

All efficacy evaluations will be performed at each 6-month clinic visit, except for echocardiograms, which will be performed every 12 months on an annual basis.

Each echocardiogram will be recorded and reviewed locally by the clinical site, and the clinical significance of the findings will be assessed by the Investigator. Each echocardiogram will also be sent to an independent imaging laboratory for centralized review of the results. Detailed instructions for performing echocardiography will be provided in a separate manual.

The 6-minute walk test will be conducted in accordance with guidelines established by the American Thoracic Society. Detailed instructions for conducting the 6-minute walk test will be provided in a separate manual.

Refer to Appendices 1, 2 and 3, respectively, for the Patient Global Assessments, NYHA classification, and KCCQ efficacy evaluation forms.

Classification of mortality and hospitalization (all cause and cardiac-related) will be determined by the Primary Investigator and the Sponsor.

7.2. Physical Examinations and Vital Signs

A complete physical examination, weight and vital signs, will be performed at the end of study visit, including assessment of the following body systems:

General appearance	Endocrine
Head and neck	Cardiovascular
Eyes	Abdomen
Ears	Skin
Nose	Musculoskeletal
Throat	Neurological
Respiratory	Immunologic/Allergies
Genitourinary	Hematologic/Lymphatic

During the trial, abbreviated physical examinations, including weight and vital signs, will assess general appearance, cardiovascular, respiratory, and gastrointestinal systems at each 6-month clinic visit.

Vital signs to be measured include lying and standing systolic and diastolic blood pressure (mmHg), lying and standing pulse (beats per minute), oral temperature (ºC), and respiration rate (breaths/minute).

7.3. Clinical Laboratory Tests

Blood samples will be collected at every 6-month visit to the clinical unit. The following clinical laboratory tests will be assessed:

Serum chemistry	
Sodium	Globulin
Potassium	Alkaline phosphatase
Chloride	Alanine aminotransferase (AST)
Bicarbonate	Aspartate aminotransferase (ALT)
Blood urea nitrogen	Gamma glutamyl transferase
Creatinine	Cholesterol
Calcium	Uric acid
Inorganic Phosphorous	Thyroid-stimulating hormone
Glucose	Total thyroxine (T4)
Total bilirubin	Free T4
Total protein	Prealbumin (transthyretin)
Albumin	Retinol-binding protein
NT-pro-BNP	Troponin I and T

Coagulation	
Prothrombin time (PT)	International normalized ratio (INR)

Note: laboratory assessment for PT and INR will not be sent to a central laboratory but will be processed by the local laboratory at each site.

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

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

7.4. Electrocardiograms

During the trial, ECGs will be performed annually every 12 months.

The site will perform ECGs in accordance with standard site practice. Ten-second rhythm strips will accompany each ECG. The ECGs will be recorded and reviewed locally by the clinical site, and the clinical significance of the findings will be assessed by the Investigator.

7.5. Adverse Events

Starting from the date the informed consent form is signed, adverse events (AEs) will be recorded in the CRF and monitored throughout the study. All adverse events should be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es). All AEs will be recorded on the CRF. Definitions, documentation, and reporting of AEs are described in Section 9.

7.6. Concomitant Medications

On Day 0, in conjunction with the review of their medical history, all subjects will be asked about the medications they are taking. Thereafter, subjects will be asked about the medications they have been taking at 3-month intervals (i.e., during clinic visits every six months and via telephone contact at 3-month intervals between clinic visits). All concomitant medications will be recorded on the CRF.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

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

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

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

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Should an investigator be made aware of any SAE occurring any time after the active reporting period, it must be promptly reported.

- AEs (serious and non-serious) should be recorded on the CRF from the time the subject has taken at least one dose of study treatment through last subject 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;
- Exposure via breastfeeding;
- Medication error.

8.4. 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.

8.5. Serious Adverse Events

An SAE 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.

8.5.1. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) concurrent with abnormal elevations in total bilirubin 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 ≥3 times the upper limit of normal (X ULN) concurrent with a total bilirubin ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase ≤2 X ULN or not available.

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

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

- **Concurrent with**

    - For subjects with pre-existing values of total bilirubin above the normal range: Total bilirubin increased by one time the upper limit of normal **or** ≥3 times the upper limit of normal (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 AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/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 subject, 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.

8.6. Hospitalization

AEs reported from studies associated with hospitalization or prolongations of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. 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, neurological floor to a tuberculosis unit).

Hospitalization does not include the following:

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

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

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

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

8.7. Severity Assessment

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

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

8.8. Causality Assessment

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

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

8.9. Exposure During Pregnancy

For investigational products and for marketed products, an exposure during pregnancy (also referred to as exposure in-utero (EIU) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or being exposed (eg, due to treatment or environmental exposure) or after discontinuing or having been directly exposed to the investigational product;

2. A male has been exposed (eg, due to treatment or environmental exposure) to the investigational product prior to or around the time of conception 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 Pfizer on an EIU Form (this is a specific version of the Serious Adverse Event Form). In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EIU Form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

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

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

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

- 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 serious adverse events when the investigator assesses the neonatal death as related or possibly related to exposure to investigational product.

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

8.10. Withdrawal Due to Adverse Events (See Also Section 6.3 Subject Withdrawal)

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

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

8.11. Eliciting Adverse Event Information

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

8.12. 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.

8.12.1. Serious Adverse Event Reporting Requirements

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

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

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

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to

allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and 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.

8.12.2. Non-Serious Adverse Event Reporting Requirements

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

8.12.3. Sponsor Reporting Requirements to Regulatory Authorities

Adverse event reporting, including suspected serious unexpected 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, which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1. Sample Size Determination

There is no formal sample size calculation for this protocol. Subjects who completed Protocol Fx1B-201 are eligible; up to 35 subjects are expected to enroll in Protocol Fx1B-303.

9.2. Efficacy Analysis

9.2.1. Analysis of Primary Endpoint

For subjects who enroll into this protocol, the cumulative efficacy data (starting from Protocol Fx1B-201) as measured by the Patient Global Assessment, NYHA classification, KCCQ, 6-minute walk test, echocardiograms, and serum levels of troponin I, troponin T, and NT-proBNP will be presented.

Baseline data from protocol Fx1B-201 will be used as baseline for these analyses.

Subjects who enroll into the study and receive any amount of investigational product will be included in the safety population. Subjects who receive any amount of investigational product and have at least one post-baseline efficacy assessment will be included in the efficacy population.

9.2.2. Patient Global Assessment

Each subject's overall quality of life, as measured by the Patient Global Assessment (Appendix 1), will be summarized using descriptive statistics. In addition, the percentage of subjects with unchanged, worsened, or improved global assessments (and 95% confidence intervals) will be presented at each scheduled assessment.

9.2.3. New York Heart Association Classification

Subjects will be evaluated using the New York Heart Association (NYHA) classification (Appendix 2). Descriptive statistics will be presented by visit for each classification: Class I, Class II, Class III, and Class IV (see Appendix 2 for definitions). The number and percentage of subjects who improved, worsened, or with no change from baseline will also be presented at each visit.

9.2.4. Kansas City Cardiomyopathy Questionnaire

The Kansas City Cardiomyopathy Questionnaire (KCCQ, Appendix 3) 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

Change from baseline for each summary score of the KCCQ will be analyzed using a mixed model analysis (with baseline value as covariate, subjects as random effect, and time as fixed effect). Data will also be summarized by each scheduled assessment and a graphical presentation of these data will be presented.

9.2.5. Six-minute Walk Test

Descriptive statistics will be presented by visit for the distance walked (in meters), the change from baseline in distance walked, the categories of distance walked (<300 meters, 300-374.9 meters, 375-449.9 meters, and ≥450 meters), and the classification of improved, no change, or worsened. Pre- and post-baseline dyspnea and fatigue values (using the Borg Scale) will be summarized by visit, as well as post-test change from baseline in dyspnea and fatigue.

9.2.6. Echocardiogram

Echocardiogram parameters will include, but are not limited to:

Interventricular septal thickness	Valvular abnormalities (thickening, regurgitation)
Posterior left ventricular wall thickness	Pericardial effusion (yes/no)
Left atrial diameter	Lateral s', e', a'
Left ventricular end diastolic diameter	Septal s', e', a'
Left ventricular mass	Tissue Doppler
Ejection fraction	Mitral deceleration time
Right ventricular wall thickness	e:e' ratio
Doppler data	E/A ratio

Each echocardiogram parameter will be compared to baseline. In addition, select echocardiogram parameters will be categorized as normal or abnormal. These classifications will be compared to baseline and assessed over time.

9.2.7. Troponin I, Troponin T, and NT-pro-BNP

Serum levels of troponin I and T, and NT-pro-BNP will be assessed at baseline and at each clinic visit. Descriptive statistics for each analyte will be presented for the actual values and the change from baseline at each clinic visit.

9.2.8. Mortality and Hospitalization

The endpoints of mortality and hospitalization (all cause and cardiac-related) will be analyzed individually and as composite measures.

A Kaplan-Meier plot of time to event from the start of Protocol Fx1B-201 will be generated, and the event rate and associated 95% confidence intervals will be presented at 1, 2, 3, and 4 years since the start of the investigational drug.

9.3. Analysis of Other Endpoints

9.3.1. Demographics and Baseline Characteristics

Demographics and baseline data (medical history, age, gender, race, weight, and height) will be summarized using descriptive statistics.

9.3.2. Physical Examination 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.

9.4. Concomitant Medication Usage

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

9.5. Safety Analysis

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

9.6. Interim Analysis

Given the lack of long-term data in TTR-CM, interim analyses will be performed during the course of the study to allow for the reporting of safety and efficacy data.

9.7. Data Monitoring Committee

This study will use a Data Monitoring Committee.

The DMC will be responsible for ongoing monitoring of the efficacy and safety of subjects in the study according to the Charter. The recommendations made by the 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 which are not endpoints, to regulatory authorities, as appropriate. In this instance, such disease-related efficacy endpoints are not reported individually as SAEs.

10. QUALITY CONTROL AND QUALITY ASSURANCE

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

The study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), 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.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

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

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

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

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

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be

retained by the investigator according to International Conference on Harmonisation (ICH), local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

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

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

12. ETHICS

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

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

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

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 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 on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

Subject names, address, birth date and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify the trial subject. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data.

The informed consent document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent document used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Pfizer before use.

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

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

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

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

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

13. DEFINITION OF END OF TRIAL

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

14. SPONSOR DISCONTINUATION CRITERIA

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

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 28 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

Publication of study results is discussed in the CSA.

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of this study on www.clinicaltrials.gov (ClinicalTrials.gov). Pfizer posts the results of all studies that it has registered on ClinicalTrials.gov regardless of the reason for registration.

The results are posted in a tabular format called Basic Results.

For studies involving a Pfizer product, the timing of the posting depends on whether the Pfizer product is approved for marketing in any country at the time the study is completed:

- For studies involving products applicable under the US Food and Drug Administration Amendments Act of 2007 (FDAAA), ie, FDA-approved products, Pfizer posts results within one year of the primary outcome completion date (PCD). For studies involving products approved in any country, but not FDA approved, Pfizer posts results one year from last subject, last visit (LSLV).

- For studies involving products that are not yet approved in any country, Pfizer posts the results of already-completed studies within 30 days of US regulatory approval, or one year after the first ex-US regulatory approval of the product (if only submitted for approval ex-US);

- For studies involving products whose drug development is discontinued before approval, Pfizer posts the results within one year of discontinuation of the program (if there are no plans for outlicensing or within two years if outlicensing plans have not completed).

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 trial concluded according to the pre-specified protocol or was terminated.

15.2. Publications by Investigators

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

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

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

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

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

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

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Appendix 1. Patient Global Assessment

Patient Global Assessment:

At Baseline, the Patient Global Assessment will be:

"In general, how do you feel today?"

- ❑ Excellent
- ❑ Very good
- ❑ Good
- ❑ Fair
- ❑ Poor

At each follow-up visit, the Patient Global Assessment will be:

"How do you feel today as compared to when we last talked with you for a study visit?"

- ❑ Markedly improved
- ❑ Moderately improved
- ❑ Mildly improved
- ❑ Unchanged
- ❑ Mildly worsened
- ❑ Moderately worsened
- ❑ Markedly worsened

Appendix 2. New York Heart Association Classification

New York Heart Association (NYHA) Classification:

Class I

Patients 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

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

Class III

Patients 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

Patients 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.

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 3. Kansas City Cardiomyopathy Questionnaire

The KC Cardiomyopathy Questionnaire

Study ID# ☐☐☐☐☐

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

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

Please place an [X] in one box on each line

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

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

My symptoms of **heart failure** have become...

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

CCI [redacted]

Study ID# ☐☐☐☐☐

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

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

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

It has been...

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

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

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

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

It has been...

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

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

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

CCI [redacted]

Study ID# ☐☐☐☐☐

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

It has been...

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

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

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

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

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

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

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

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

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

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

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

CCI [redacted]

Study ID# ☐☐☐☐☐

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

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

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

Please place an [X] in one box on each line

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

CCI [redacted]

[redacted]