A STUDY TO CHARACTERIZE THE SAFETY AND EFFICACY OF TAFAMIDIS ONCE DAILY IN THE TREATMENT OF TRANSTHYRETIN AMYLOID CARDIOMYOPATHY IN CHINESE PARTICIPANTS

Investigational Product Number:	PF-06291826
Investigational Product (Study Intervention) Name:	Tafamidis free acid
United States (US) Investigational New Drug (IND) Number:	(N/A)
European Clinical Trials Database (EudraCT) Number:	(N/A)
Protocol Number:	B3461077
Phase:	4

Short Title: A study to assess the safety and efficacy of tafamidis in Chinese participants with ATTR-CM

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
Original protocol	28 June 2019	Not applicable (N/A)
Amendment 1	26 March 2021	**Short Title:** The short title was **modified** as *A study to assess the safety and efficacy of tafamidis in Chinese participants with ATTR-CM* to be more consistent with the protocol title. **Investigational Product Number:** *PF-06291826-00* was **changed** to *PF-06291826* for correction. *with or without Troponin T* or *with or without TnT* was **deleted** in the sections below. • **1.3. Schedule of Activities (SOA)** • **8. STUDY ASSESSMENTS AND PROCEDURES** • **9.4.3.2 TnI w/o TnT** • **Table 1 Protocol-Required Safety Laboratory Assessments** • **10.10 Appendix 10: Abbreviation** **Rationale:** troponin will be tested at the central lab for this study, and only Troponin I will be tested. **Section 1.1 Synopsis:** • *In China, in order to facilitate ATTR-CM patient convenience, the proposed clinical dosing regimen is a 61 mg tafamidis soft capsule orally once daily,with or without food* was **changed** to *In China, tafamidis meglumine capsule 20 mg once daily has already been approved for the treatment of ATTR-PN in adult patients with stage 1 symptomatic polyneuropathy in February 2020; 61 mg tafamidis soft capsule orally once*

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		daily was approved in September 2020 for the treatment of ATTR-CM, because both tafamidis 61 mg and tafamidis meglumine 20 mg was approved in China. • *Post-study follow-up (28 days after End of Study Visit)* was **changed** to *Post-treatment follow-up* for clarity. • *We plan to begin the enrollment within 6 months of the approval of tafamidis for ATTR-CM by China Health Authority. The enrollment duration is 16 months* was **deleted** to add some flexibility for recruitment. The same wording was also **deleted** in **Section 4.1 Overall Design.** • *Early study discontinuation* was changed to *End of Treatment* to align with the study endpoints. The same change was also made in **Section 1.3 Schedule of Activities (SOA) and 4.1 Overall Design.** **Section 1.3. Schedule of Activities (SOA)**: • *Post-study follow-up (28 days after End of Study Visit)* was **changed** to *Post-treatment follow-up (28 +7 days after last dose)* for clarity. • *Early study discontinuation* was **change** to *within 2 weeks after End of Treatment* for clarification. • *X* was **added** at Month 1 and *X* was removed at Month 12 for Dispense investigational drugs to be consistent with Section 6.1

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		• *Bisphosphonate* was **deleted** from SoA, note c, and throughout the protocol • In note c, *documented previously* was **changed** to *documented within 5 yea rs of enrollment. If greater than 5 years, biopsy or radionuclide bone scintigraphy (99mTc-PYP) must be repeated at the investigative site* to ensure the diagnosis more accurate. • In note g, *within 5 years of enrollment* was **added** at the end of this sentence to ensure the diagnosis is more accurate. **Section 5.2 Exclusion criteria:** *(or vaccine)* was **added** after *Previous administration with an investigational drug* in item 4 for clarification. **Section 6.1.1 Administration:** some specific instructions of tafamidis administration related procedures and notes were **moved** here from Section 8 with some minor revisions for clarity purpose. **Section 6.5 Concomitant Therapy:** • *If a participant is offered, in accordance with the prevailing local guidelines, a COVID-19 vaccine, it should be permitted. This would be recorded as a concomitant medication and standard AE collection and reporting processes would be followed* was **added** at the end of third paragragh in this section for clarification. • *Permitted NSAIDs include* was **changed** to *Chronic use (greater than 4 times/month) of NSAIDs before the*

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		study is prohibited except the following permitted NSAIDs in item 1. Because some NSAIDs can affect the Pharmacokinetic and Pharmacodynamic results of tafamidis. • *Topical ophthalmic NSAIDs administered while the patient's nasal punctum is occluded are also permitted* was **added** in item 1 of *Prohibited Therapies* to add some flexibility for concomitant therapies. • Item 3 of *Prohibited Therapies* was **updated** as *Additionally, the use of diflunisal, tauroursodeoxycholate and doxycycline or any other TTR stabilizing agent or experimental interventions for transthyretin amyloid cardiomyopathy within 30 days prior to the study entry and/or during study participation is not permitted*. Because the use of diflunisal or any other TTR stabilizing agent or experimental interventions for ATTR-CM within 30 days prior to the study entry or during the study is also prohibited. • *5. Use of any dosage form of tafamidis before the study is prohibited* was **added** in *Prohibited Therapies*. Because this study would only include tafamidis naive patients as mentioned in section 4.1 Overall Design. Because any prior use of tafamidis before the study participation may affect the assessments related to the study endpoints. **Section 7.1 Discontinuation of Study Intervention:**

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		• *If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for the End of Treatment visit (within 2 weeks after the End of Treatment date). See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.* was **added** per the new template. • *In the event of Early Study Discontinuation, the site staff will follow-up on the participant's vital status 12 months (or early study discontinuation) from baseline* was **changed** *to In the event of early Study Intervention Discontinuation, the site staff will follow-up on the participant's vital status at Month 12 from baseline (or at Early Study Discontinuation visit for a participant who withdraws consent for any further contact)* for clarification purpose. • *In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.* was **added** per the new template. • *QTcB* was **deleted** throughout the protocol, because in the new template QTcB was not recommended to use.

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		Section 7.2. Participant Discontinuation/Withdrawal From the Study: • The criteria for withdraw from the study and the data management for these participants was **changed** as per updated template. • *At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and followup and for any further evaluations that need to be completed. The early discontinuation visit applies only to participants who are enrolled/randomized and then are prematurely withdrawn from the study.* was **deleted**, because the requirement was added in **Section 7.1** in the event of end of treatment. A New ***Section 7.2.1 Withdrawl of consent*** was **added** as per updated template. **Section 8. STUDY ASSESSMENTS AND PROCEDURES :** • Suggested chronology of events was **added** where multiple procedures are scheduled at the same nominal time point(s) relative to dosing to clarify the appropriate sequence. • *Post-study follow-up* in this section was both **changed** to *Post-treatment follow-up*, for clarification purpose. • The specific procedures for every visit was **deleted** because the procedures for every visit were already in SOA or

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		moved to Section 6.1.1 Administration for clarity. The paragragh of blood collection volume was **updated** as *The total planned per protocol blood sampling volume for individual participants in this study is approximately 280 mL, including potential additional blood samples taken for safety assessments at times specified by investigator. Additional blood samples may be taken for safety assessments when required for management of adverse events, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days. In exceptional circumstances, such as medical emergencies, this volume may be exceeded and will not constitute a protocol deviation in such circumstances.***Section 8.3. Adverse Events and Serious Adverse Events:*** *Each participant/legally authorized representative will be questioned about the occurrence of AEs in a nonleading manner* was **added** as per updated template. **Section 8.3.1. Time Period and Frequency for Collecting AE and SAE Information:** The section was **updated** per the new protocol template with more specific requirement to define the period and process for collecting AE and SAE information. **Section 8.3.1.1. Reporting SAEs to Pfizer Safety:** The section was **updated** per the new protocol template with more specific

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		requirement to report SAEs to Pfizer Safety. **Section 8.3.1.2. Recording Nonserious AEs and SAEs on the CRF:** *All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF* **was added as** per updated template. *During the active collection period, both nonserious AEs and SAEs are recorded on the CRF* **was changed to** *The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant as per updated template.* **Section 8.3.4. Regulatory Reporting Requirements for SAEs:** *an investigator safety report* **was changed to** *SUSARs* as per updated template. *investigator's brochure* **was changed to** *SRSD(s)* as per updated template. **Section 8.3.5.1. Exposure During Pregnancy:** The whole section was **updated** per the new protocol template with more specific requirement to report and manage an EDP for investigators. **Section 8.3.5.2. Exposure During Breastfeeding:** This new section was **added** per the new protocol template with very specific requirement to report and manage an exposure during breastfeeding for investigators.

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		Section 8.3.5.3. Occupational Exposure: The whole section was **updated** per the new protocol template with more specific requirement to report and manage an occupational exposure for investigators. New sections were **added** as per updated template as following: • ***Section 8.3.8. Adverse Events of Special Interest*** • ***Section 8.3.8.1. Lack of Efficacy*** • ***Section 8.3.9. Medical Device Deficiencies*** • ***Section 8.3.9.1. Time Period for Detecting Medical Device Deficiencies*** • ***Section 8.3.9.2. Follow up of Medical Device Deficiencies*** • ***Section 8.3.9.3. Prompt Reporting of Device Deficiencies to Sponsor*** • ***Section 8.3.9.4. Regulatory Reporting Requirements for Device Deficiencies*** **Section 8.3.10. Medication Errors:** *be notified within immediately* was **changed** to *be notified within 24 hours* as per updated template. **Section 8.4 Treatment of Overdose:** The whole section was **updated** per the new protocol template. **Section 8.5 Pharmacokinetics:** *or for other internal exploratory purposes* was **deleted**, because no exploratory tests will be done in this study. Section **8.6 Pharmacodynamics:**

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		• *The actual date and time (24-hour clock time) of each sample will be recorded* was **added** for clarification. • *as well as for other internal exploratory purposes* was **deleted**, because no exploratory tests will be done in this study. **Section 8.10 Biopsy Documentation of Amyloid:** • *Or other analysis can be utilized to confirm the deposit of amyloid* was **added** behind *Congo red stain*, to add some flexibility for the acceptable biopsy analysis methods for the confirmation of amyloid deposition. • *For purposes of this study, an existing biopsy result will be considered valid if it is documented in writing and the biopsy was performed within 5 years of study enrollment. If the biopsy is not valid, it will be repeated as a screening procedure at the investigational site.* was **added** as the last paragraph of this section to ensure the diagnosis is more accurate. **Section 9.4.2 Pharmacodynamics Analyses: TTR Concentration and TTR Stabilization:** • The section title was **changed** from ***TTR Stabilization*** to ***Pharmacodynamics Analyses: TTR Concentration and TTR Stabilization,*** because TTR concentration is also analysed in the study.

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		• The content of all the 1st to 3rd paragraph was **deleted**, and *The TTR concentration and percent TTR stabilization will be determined. Declaring a participant to have been "stabilized" is defined as percent stabilization is equal to or more than 32%.* was **added** as the detailed calculation methods is not needed in protocol. • The last paragragh was **updated** as *All pharmacodynamic analyses will be performed on the PD population. TTR concentration and percent stabilization will be summarized descriptively as continuous measures, by visit, for overall, by TTR genotype, and by NYHA baseline classification. The proportion of participants who achieve TTR stabilization (ie, who has been stabilized) and its 95% confidence interval will be calculated and summarized, as categorical measure, at each post-baseline time point, for overall, by TTR genotype, and by NYHA baseline classification* to add in the descriptive analysis of TTR concentration and percent stabilization. **Section 10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting:** *investigational product* was **changed** to *study intervention* in the whole section per the new template, the same change was also made in Section 10.4 and 10.5. **Section 10.3.1. Definition of AE:**

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		Any abnormal laboratory test results that meet some of the conditions which must be recorded as an AE was **added** in this section per the new protocol template. **Section 10.3.2. Definition of SAE:** Suspected transmission via a Pfizer product was **added** as an SAE in item *f. other situations* per the updated template. **Section 10.3.3. Recording/Reporting and Follow up of AEs and/or SAEs:** *None* was **changed** to *All AEs/SAEs associated with exposure during pregnancy or breastfeeding. Occupational exposure is not recorded* as per updated template. *Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure* was **added** as per updated template. **Section 10.4.4 Contraception Methods:** All the content under the title of **Collection of Pregnancy Information** was **deleted** because this was all included in the new added **Section 8.3.5.1 Exposure During Pregnancy**. A new **Section 10.10 Appendix 10: Alternative Measures During Public Emergencies** was **added** per the requirement of new protocol template. *Gelatin* in the drug names was all **deteled** in the protocol to be consistent with the approved label of Tafamidis 61 mg and Tafamidis meglumine 20 mg.

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		Editorial, grammatical, formatting, and administrative changes were made throughout the document.

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A study to assess the safety and efficacy of tafamidis in Chinese participants with ATTR-CM

Rationale

Transthyretin amyloid cardiomyopathy (ATTR-CM) occurs when transthyretin (TTR) amyloid fibrils infiltrate the myocardium, leading to deposits of extracellular amyloid. Deposition of transthyretin fibrils occurs between the myocardial cells and produces a thickening and stiffening of the myocardial tissue. This infiltration of the myocardium results in diastolic dysfunction progressing to restrictive cardiomyopathy, congestive heart failure, and ultimately death. There is a high unmet need to treat transthyretin amyloid cardiomyopathy, which is a life threatening, rare disease. Only 60 Chinese cardiac amyloidosis case reports were published from 2002-2017, and ATTR-CM is extremely rarely reported.[1-7] One of 60 cases was diagnosed as ATTR-CM,[6] 2 of them were just suspected one.[2]

Tafamidis is considered as a disease modifying therapy for TTR amyloid diseases. It binds to the thyroxine binding sites on the TTR tetramer, thereby preventing destabilization into the monomeric form which can form amyloid fibrils deposited into the extracellular space.

ATTR-CM is listed in 1st Chinese Rare Disease list released in 2018 under Idiopathic Cardiomyopathy category. Based on China regulatory regulation on encouragement for rare disease medication development, Pfizer plans to bridge the pivotal study efficacy and safety data and Japanese pharmacokinetic (PK) data to apply for conditional approval with a post approval commitment study design.

Study B3461016 (Fx1A-105) was a Phase 1 study of 20 mg of tafamidis meglumine PK in mild or moderate hepatic impairment participants and age, weight, and gender-matched healthy volunteers. The results indicated dosage adjustment is not necessary in participants with mild to moderate hepatic impairment. Study B3461009 was a Phase 1 study to evaluate the safety, tolerability, PK and pharmacodynamics (PD) of PF-06291826 (tafamidis meglumine) after single oral administration of 20 mg and 40 mg tafamidis meglumine soft capsules to Japanese and Western healthy participants. Mean PK parameters and PD results (TTR percent stabilization) of Japanese participants were similar to those in Western participants suggesting that there are no PK and PD differences based on ethnicity.

The potential for enzymatic and transporter mediated tafamidis drug-drug interaction (DDI) was evaluated at the projected clinical tafamidis doses of 20 mg/day tafamidis meglumine and 61 mg/day tafamidis free acid doses in multiple nonclinical and one clinical drug-drug interaction (DDI) study (B3461018 [Fx1A-109]). Results from these studies have found that the potential for clinically significant PK drug-drug interactions with tafamidis is low.

Based upon the TTR % stabilization data from Study B3461040, a Phase 1, randomized, double-blind, crossover, ascending dose escalation study to assess the safety and PK of tafamidis meglumine doses greater than 120 mg as oral solution in healthy participants, tafamidis meglumine doses of 20 and 80 mg were used in the international Phase 3 pivotal study B3461028. Study B3461028 was a Phase 3, multicenter, international, 3-arm, parallel design, placebo-controlled, randomized study with a 30 month double-blind treatment phase, to determine the efficacy, safety, and tolerability of tafamidis meglumine in ATTR-CM patients with either variant or wild-type TTR. A clinically relevant, statistically significant (p=0.0006) reduction of 30% in all-cause mortality and frequency of cardiovascular (CV)-related hospitalizations at 30 months was demonstrated for patients treated with tafamidis meglumine compared to those treated with placebo. This benefit was further reflected consistently and robustly in key secondary and exploratory analyses. Tafamidis treatment was generally safe and well tolerated in the study participant population, with an average age of 74, with few dose reductions and a similar frequency of treatment-emergent adverse events (TEAEs) and serious TEAEs between the treatment groups. The majority of the adverse events (AEs) were mild or moderate in severity and discontinuation due to AEs, both permanent and temporary, were less common in the tafamidis groups than in the placebo group. The results of pivotal Phase 3 study B3461028 demonstrated that comparable treatment effects were observed for the primary analyses (all-cause mortality and the frequency of cardiovascular-related hospitalizations) and secondary analyses (including TTR stabilization at Month 1) when analyzed by dose (20 mg and 80 mg). Posthoc analyses of cardiac biomarker data prognostic of survival (NT-proBNP) and CV related hospitalizations (Troponin I) favor the 80 mg dose. Study B3461028 enrolled 17 (of 441) participants in Japan (5 participants in the placebo group, 2 participants in the tafamidis meglumine 20 mg group, ten participants in the tafamidis meglumine 80 mg group). The sub-analysis of primary and key secondary endpoint data from these Japanese participants indicate no apparent trends that deviated from the overall test population.

A recent analysis of available survival data from Study B3461045, an ongoing, long-term extension study for participants previously enrolled in study B3461028, suggest a meaningful 10.2% reduction in risk of death (Hazard ratio 0.8976, 95% CI 0.5711, 1.4108) in patients on 80 mg compared to 20 mg of tafamidis meglumine over the longer period of treatment (p=0.6395). These results supported the dose recommendation of 80 mg tafamidis meglumine.

These points summarize the evidence supporting the expectation that the tafamidis meglumine clinical profile in the Chinese population will be consistent with the global population and is largely derived from experience with Japanese patients.

To facilitate patient convenience, the sponsor has developed a single 61 mg tafamidis free acid (called as tafamidis in the texts hereafter, PF-06291826) soft capsule, instead of 4 20 mg tafamidis meglumine soft gel capsules (one capsule contains 12.2 mg tafamidis, the active pharmaceutical ingredient). A single 80 mg tafamidis meglumine soft gel capsule is technically not feasible because of a concentration-dependent gelling of tafamidis meglumine. A bioequivalence (BE) study, B3461056, was conducted and showed

bioequivalence between 80 mg (4 x 20 mg) tafamidis meglumine with 61 mg tafamidis at steady-state.

Tafamidis meglumine capsule 20 mg once daily has already been approved in the European Union for the treatment of Transthyretin Amyloid Polyneuropathy (ATTR-PN) in adult patients with stage 1 symptomatic polyneuropathy in 2011. In Japan, tafamidis meglumine 20 mg soft capsule once daily has also been approved by the Ministry of Health, Labor and Welfare (MHLW) to delay the peripheral neurological impairment of transthyretin familial amyloid polyneuropathy in September 2013, and tafamidis meglumine 4 x 20 mg soft capsule once daily approved to delay the progression of ATTR-CM in March 2019. Tafamidis meglumine 4 x 20 mg once daily and tafamidis 61 mg have been approved in the United States in May 2019 for the treatment of the cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization. Tafamidis has been approved in Europe in February 2020 for the treatment of ATTR-CM. In China, tafamidis meglumine capsule 20 mg once daily, with or without food, has already been approved for the treatment of ATTR-PN in adult patients with stage 1 symptomatic polyneuropathy in February 2020; 61 mg tafamidis soft capsule orally once daily, with or without food, was approved in September 2020 for the treatment of ATTR-CM.

The safety profile of tafamidis meglumine for the treatment of ATTR-CM has been evaluated in 377 ATTR-CM patients in the pivotal Phase 3 Study B3461028 and its ongoing long-term extension (LTE) Study B3461045, as well as in the Phase 2 Study B3461025 and the associated ongoing LTE, Study B3461026 (data provided for both ongoing LTEs through cutoff date of 01 August 2018). Tafamidis safety data are also presented from 17 Phase 1 studies 348 healthy participants, as well as a Phase 1 study in participants with hepatic impairment. Additional supportive safety data are provided from 5 clinical studies (cutoff date 03 January 2017) involving ATTR-PN patients (n=137) and post-marketing data (cutoff date 01 August 2018), as well as safety data from tafamidis-treated patients enrolled in Study B3461001 (Transthyretin-Associated Amyloidosis Outcomes Survey [THAOS]; cutoff date 01 August 2018).

Tafamidis was shown to be safe and well-tolerated. No adverse drug reactions were identified with tafamidis administration in the ATTR-CM patient population.

China Health Authority has provided guidance on the design of the post approval commitment study. A prospective observational, single-arm cohort study was suggested to evaluate adverse events. The study is to collect TEAEs observed in previous ATTR-CM studies, defined as AEs with a small numeric higher incidence observed in the tafamidis treatment group compared with placebo; noted as AEs of clinical importance for treatment with tafamidis.

The purpose of this study is to collect safety, descriptive efficacy, PK and PD of tafamidis data in Chinese ATTR-CM patients, following the approval of tafamidis 61 mg soft capsule orally once daily, with or without food, for ATTR-CM indication in China.

Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
• To characterize the safety profile of tafamidis once daily for the treatment of Chinese ATTR-CM patients in clinical practice.	• Not applicable.	• Incidence of treatment-emergent adverse events.
Secondary:		**Secondary:**
• To characterize the descriptive efficacy of tafamidis once daily in Chinese ATTR-CM patients • To characterize tafamidis PD in Chinese ATTR-CM patients. • To characterize the impact on quality of life of tafamidis once daily for the treatment of Chinese ATTR-CM patients. • To characterize tafamidis PK in Chinese ATTR-CM patients.	• Not applicable.	• Assessment of 6-MWT, NT-pro BNP at scheduled visits. • TTR stabilization and TTR concentration at Baseline (pre dosing) on Day 1, at Months 1, 6, and 12 (or End of Treatment (EOT)). • Kansas City Cardiomyopathy Questionnaire overall summary scores, EQ-5D-5L index scores and EQ-5D VAS scores, 12-Item Short Form Survey (SF-12) scores, at Day 1, Months 6, 12 (or End of Treatment (EOT)). • PK: plasma concentrations of tafamidis at Months 1, 6, and 12 (or EOT).

Overall Design

This is a national, multi-center, single-arm study, open-label to patients with symptomatic ATTR-CM who are tafamidis naïve. This study is to obtain safety, descriptive efficacy, PK and PD data for tafamidis 61 mg soft capsule orally once daily, with or without food. Participants with New Year Heart Association (NYHA) class greater than or equal to III should not make up more than 1/3 of all enrolled participants

Investigators will confirm the eligibility of each participant to meet inclusion/exclusion criteria. Participant eligibility for participation in the study will receive tafamidis 61 mg once daily or 12 months following the assessment as the screening and baseline, month 1, 3, 6, 9 and 12 visits (or End of Treatment visit).

Patients will continue to receive their current medications and all other standard care for their disease. The use of permitted concomitant medication must be in accordance with approved tafamidis package insert. Concomitant medication not permitted in this study is described in Section 6.5.

Participants will complete protocol required tests and procedures as described in schedule of activities. A final study report will be completed approximately 3 years after the date of the first tafamidis patient enrollment in the study.

Scheduled Visits: Day 1, Months 1, 3, 6, 9,12 (or End of Treatment) and a Post-treatment follow-up.

Number of Participants

At least 53 participants need to be treated. Refer to Section 9.2 for detailed information on sample size determination.

Intervention Groups and Duration

Total duration of study participation for each participant receiving tafamidis once daily with approved dose is 12 months (or Early Study Discontinuation). Follow-up visit dates should be based on the date of the Baseline visit.

Data Monitoring Committee:

The study will not use an data monitoring committee (DMC).

Statistical Methods

In order to attain an 80% probability of observing at least 1 participant having an event for TEAEs with incidence rate of 3%, at least 53 participants need to be treated.

Descriptive analyses will be performed.

1.2. Schema

Not applicable.

1.3. Schedule of Activities (SoA)

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

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

Procedure/ Assessment	Screening	Baseline visit	Month[a]					
	Day-45 to Day 0	Day 1	1 (±1 week)	3 (Telephone visit ±2 weeks)	6 (±2 weeks)	9 (Telephone visit ±2 weeks)	12 (±2 weeks) (or within 2 weeks after End of Treatment)	Post-treatment follow-up (28+7 days after last dose)
Informed Consent	X							
Medical History	X							
Review entrance criteria	X	X						
Full physical examination	X							
Brief physical examination		X	X		X		X	
Height	X							
Weight	X	X	X		X		X	
12 Lead ECG	X	X	X		X		X	
Vital signs[b]	X	X	X		X		X	
Echocardiogram	X				X		X	
Tissue biopsy or radionuclide bone scintigraphy (99mTc-PYP)[c]	X							
Laboratory samples								
Hematology	X		X		X		X	
Serum Chemistry	X		X		X		X	
Coagulation (INR, PT, APTT,FIB)	X		X		X		X	
Thyroid-stimulating hormone, total Thyroxine 4 and free Thyroxine 4		X	X		X		X	
Retinol Binding Protein		X			X		X	
Contraception check[d]	X			X	X	X	X	X
Pregnancy test (only for WOCBP)[e]	X				X		X	
Serology (HBsAg, anti- HCV, anti-TP and anti-HIV)	X							
Serum/urine test for primary amyloidosis (AL)	X							

Procedure/ Assessment	Screening	Baseline visit	Month[a]					
	Day-45 to Day 0	Day 1	1 (±1 week)	3 (Telephone visit ±2 weeks)	6 (±2 weeks)	9 (Telephone visit ±2 weeks)	12 (±2 weeks) (or within 2 weeks after End of Treatment)	Post-treatment follow-up (28+7 days after last dose)
Mass spectrometry/ Immunohistochemistry[f]	X							
Genotyping[g]	X							
Urinalysis	X		X		X		X	
NT – proBNP, Troponin I		X			X		X	
6-MWT		X			X		X	
TTR stabilization, TTR concentration[h]		X	X		X		X	
Tafamidis concentrations[i]			X		X		X	
KCCQ[j]		X			X		X	
EQ-5D-5L[k]		X			X		X	
SF-12[k]		X			X		X	
NYHA classification	X	X			X		X	
Concomitant treatments	X	X	X	X	X	X	X	
Serious and nonserious adverse event monitoring	X	X	X	X	X	X	X	X
Hospitalization determination		X	X	X	X	X	X	
Documentation of vital status		X	X	X	X	X	X	
Record time of dosing		X	X		X		X	
Record dosing adherence			X		X		X	
Dispense investigational drugs		X	X		X			

a. Visits, if applicable, are typically defined with respect to the Baseline visit and in accordance with expectations on the standard of care and/or required procedures for the study.

b. Systolic and diastolic blood pressure (semisupine at least 5 minutes prior to assessment). pulse rate, respiratory rate and body temperature

c. Biopsy or radionuclide bone scintigraphy (99mTc-PYP) for amyloid documentation must be performed at Screening or have been performed and documented within 5 years of enrollment. If greater than 5 years, biopsy or radionuclide bone scintigraphy (99mTc-PYP) must be repeated at the investigative site.

d. Refer to Appendix 4 for Contraceptive Guidance and Collection of Pregnancy Information.

e. For women of childbearing potential. Refer to Appendix 4 for Woman of Childbearing Potential (WOCBP).

f. For those absence of a variant TTR genotype, absence of radionuclide bone scintigraphy (99mTc-PYP) and presence of amyloid deposits in biopsy tissue.

g. Repeat not required if there is documentation of genotyping result confirming the TTR gene mutation within 5 years of enrollment.

h. TTR stabilization and TTR concentration: baseline (Day 1) sample: collect pre-dose during the clinic visit. Month 1 sample: collect pre-dose and at 3 hours (±1.5 hours) post-dose. Month 6 sample: collected at

Procedure/ Assessment	Screening	Baseline visit	Month[a]					
	Day-45 to Day 0	Day 1	1 (±1 week)	3 (Telephone visit ±2 weeks)	6 (±2 weeks)	9 (Telephone visit ±2 weeks)	12 (±2 weeks) (or within 2 weeks after End of Treatment)	Post-treatment follow-up (28+7 days after last dose)

7 hours (±2.5 hours) post-dose. Month 12 sample: collect at 1 hour (±30 minutes) post-dose, or End of Treatmentsample: collect at time during the clinic visit. Please refer to Section 8.6 for details.

i. Tafamidis concentrations: Month 1 tafamidis concentration sample: collect pre-dose and at 3 hours (±1.5 hours) post-dose; Month 6 tafamidis concentration sample: collect at 7 hours (±2.5 hours) post-dose; Month 12 sample: collect at 1 hour (±30 minutes) post-dose, or End of Treatment sample: collect at time during the clinic visit. Please refer to Section 8.5 for details.

j. Kansas City Cardiomyopathy Questionnaire (KCCQ) should be completed before the EQ-5D-5L.

k. EuroQoL-5 Dimensions (EQ-5D-5L) and SF-12 to be completed after the KCCQ.

2. INTRODUCTION

2.1. Study Rationale

ATTR-CM is listed in 1st Chinese Rare Disease list released in 2018 under Idiopathic Cardiomyopathy category. Based on China regulatory regulation on encouragement for rare disease medication development, Pfizer plans to bridge the pivotal efficacy and safety data and Japanese pharmacokinetic (PK) data to apply for conditional approval with a post approval commitment study design.

Tafamidis is a small molecule that has been demonstrated to stabilize transthyretin. meglumine 20 mg soft capsule taken orally once daily has already been approved in the European Union for the treatment of Transthyretin Amyloid Polyneuropathy (ATTR-PN) in adult patients with stage 1 symptomatic polyneuropathy in 2011. In Japan, tafamidis meglumine 20 mg soft capsule once daily has also been approved by the Ministry of Health, Labor and Welfare (MHLW) to delay the peripheral neurological impairment of transthyretin familial amyloid polyneuropathy in September 2013, and tafamidis meglumine 4 x 20 mg once daily approved to delay the progression of Transthyretin Amyloid Cardiomyopathy (ATTR-CM) in March 2019. Tafamidis meglumine 4 x 20 mg once daily and tafamidis 61 mg have been approved in the United States in May 2019 for the treatment of the cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization. Tafamidis has been approved in Europe in February 2020 for the treatment of ATTR-CM. In China, tafamidis meglumine capsule 20 mg once daily has already been approved for the treatment of ATTR-PN in adult patients with stage 1 symptomatic polyneuropathy in February 2020; 61 mg tafamidis soft capsule orally once daily was approved in September 2020 for the treatment of ATTR-CM.

The purpose of the study is to collect safety, descriptive efficacy, PK, and PD of tafamidis data in Chinese ATTR-CM patients, following the approval of tafamidis 61 mg for ATTR-CM indication in China.

2.2. Background

ATTR-CM occurs when transthyretin (TTR) amyloid fibrils infiltrate the myocardium, leading to deposits of extracellular amyloid. Deposition of transthyretin fibrils occurs between the myocardial cells and produces a thickening and stiffening of the myocardial tissue. This infiltration of the myocardium results in diastolic dysfunction progressing to restrictive cardiomyopathy, congestive heart failure, and ultimately death. There is a high unmet need to treat transthyretin amyloid cardiomyopathy, which is a life threatening, rare disease. Only 60 Chinese cardiac amyloidosis case reports were published from 2002-2017, and ATTR-CM is extremely rarely reported.[1-7] One of 60 cases was diagnosed as ATTR-CM,[6] 2 of them were just suspected one.[2]

China Health Authority has released guidance on PAC study design of the post approval commitment study. A prospective observation study, single-arm cohort study is suggested to evaluate adverse events and other related safety risks. The study is to collect TEAEs that

were observed in previous ATTR-CM studies, defined as AEs with a small numeric higher incidence observed in the tafamidis treatment group compared with placebo; noted as AEs of clinical importance for treatment with tafamidis.

2.2.1. Clinical Overview

Tafamidis is an oral small molecule, under development by Pfizer, as a disease modifying therapy for TTR amyloid diseases. It binds to the thyroxine binding sites on the TTR tetramer, thereby preventing destabilization into the monomeric form which can deposit as amyloid fibrils in the extracellular space. It has been demonstrated to bind selectively to TTR (also referred to as pre-albumin) in human blood and slow fibril formation in vitro. It binds to the 2 thyroxine binding sites with negative cooperativity, exhibiting dissociation constants of 2 nM [K_{d1}] and 154 nM [K_{d2}] and kinetically stabilizing the TTR tetramer when bound (Sekijima 2009).[3]

Study Fx1A-105 (B3461016) was a Phase 1 study of tafamidis meglumine PK in mild or moderate hepatic impairment participants and age, weight, and gender-matched healthy volunteers. The results indicated dosage adjustment is not necessary in participants with mild to moderate hepatic impairment. Study B3461009 was a Phase 1 Study to evaluate the safety, tolerability, PK and pharmacodynamics (PD) of PF-06291826 (tafamidis meglumine) after single oral administration of 20 mg and 40 mg tafamidis meglumine soft capsules to Japanese and Western healthy participants. Mean PK parameters and PD results (TTR percent stabilization) of Japanese participants were similar to those in Western participants thus suggesting no significant ethnic differences in PK and PD.

The potential for enzymatic and transporter mediated tafamidis drug-drug interaction (DDI) was evaluated at the projected clinical tafamidis doses of 20 mg/day tafamidis meglumine and 61 mg/day tafamidis free acid (called as tafamidis in the texts hereafter) doses in multiple nonclinical and one clinical drug-drug interaction (DDI) study (Fx1A-109 [B3461018]). Results from these studies have found that the potential of clinically significant PK drug-drug interactions with tafamidis is low.

Study Fx-002 (B3461015) was a Phase 1 study designed to evaluate the safety, tolerability, and pharmacokinetics of orally administered tafamidis in healthy male and female volunteers at single doses up to 120 mg and 3 multiple escalating doses (15, 30 and 60 mg) administered as solution in comparison to placebo once daily over 14 days. Study Fx1A-109 was a Phase 1 study in healthy volunteers designed to evaluate the cytochrome P450 induction potential of tafamidis 20 mg administered for 14 days. In Fx-002, the mean (standard deviation) maximum observed drug concentration (C_{max}) value on Day 14 for the 60 mg solution was 4.40 (1.16) µg/mL. The mean (standard deviation) C_{max} on Day 14 for the 20 mg capsule was 2.66 (0.55) µg/mL in Fx1A-109.

There were no dose-limiting safety or tolerability issues noted during the Phase 1 program in healthy participants up to a single dose of 480 mg or multiple doses up to 60 mg. Further, a single oral dose of 20 mg tafamidis was well tolerated by participants with moderate or mild hepatic impairment. During Study B3461045, 2 patients experienced an acute overdose.

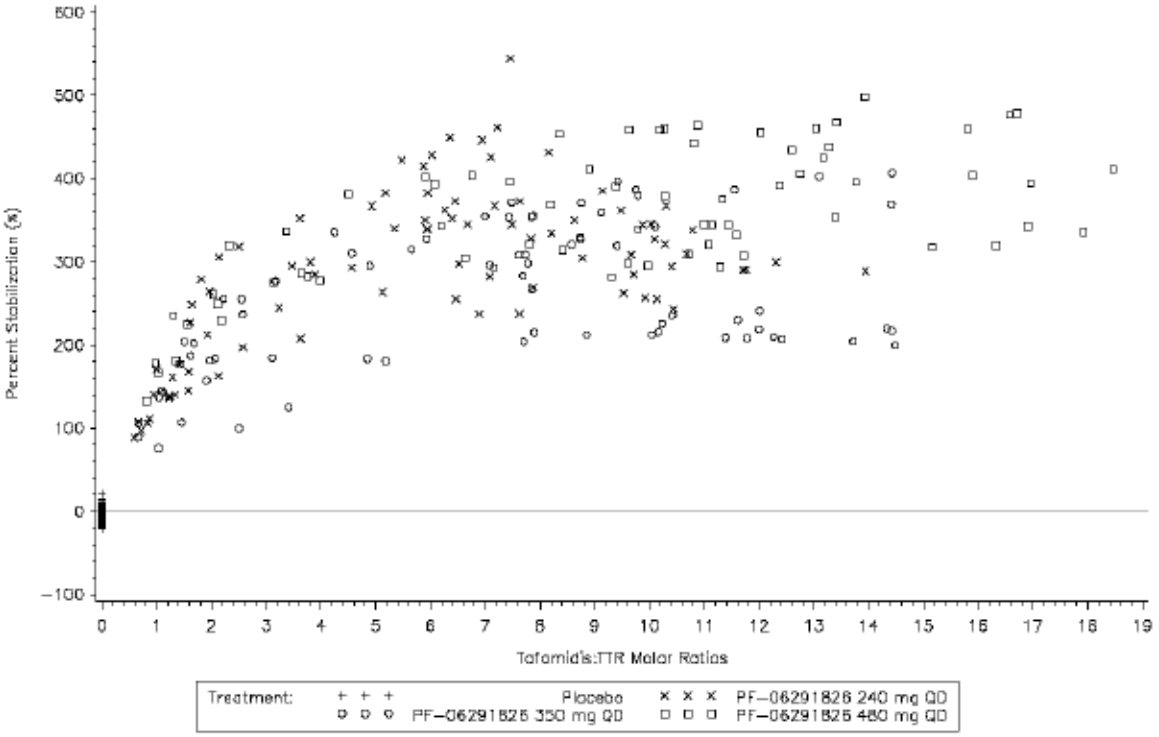
Both involved the accidental ingestion of a single tafamidis dose of 160 mg without the occurrence of any associated adverse events .

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

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

In order to calculate molar ratios at various tafamidis exposures, a TTR concentration must be assumed. Mean TTR concentrations observed at baseline in Study Fx-005 (B3461020) (24.7 mg/dL) and in patients with V122I mutations in Study Fx1B-201 (13.5 mg/dL) and the Transthyretin Amyloid Cardiac Study (TRACS) (14.9 mg/dL) are assumed for the calculations that follow: a 20 mg QD tafamidis dose at steady state produces a mean MR in the range of 1.2 to 3.2 from mean minimum drug concentration at steady state ($C_{min,ss}$) to maximum drug concentration at steady state ($C_{max,ss}$), which is below the plateau region of the data depicted in (Figure 1). Mean $C_{min,ss}$ to $C_{max,ss}$ following tafamidis doses of 80 mg are expected to produce MR values of 3.5 to 9.6, which are approaching or on the plateau region of TTR % stabilization.

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



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

Based upon the TTR % stabilization data, tafamidis meglumine doses of 20 and 80 mg were used in the international Phase 3 pivotal study B3461028.

Study B3461028 was a Phase 3, multicenter, international, 3-arm, parallel design, placebo-controlled, randomized study with a 30 month double-blind treatment phase, to determine the efficacy, safety, and tolerability of tafamidis meglumine in ATTR-CM patients with either variant or wild-type TTR. A clinically relevant, statistically significant (p=0.0006) reduction of 30% in all-cause mortality and frequency of CV-related hospitalizations at 30 months was demonstrated for patients treated with tafamidis meglumine compared to those treated with placebo. This benefit was further reflected consistently and robustly in key secondary and exploratory analyses. Tafamidis treatment was generally safe and well tolerated in the study participant population, with an average age of 74, with few dose reductions and a similar frequency of TEAEs and serious TEAEs between the treatment groups. The majority of the AEs were mild or moderate in severity and discontinuation due to AEs, both permanent and temporary, were less common in the tafamidis groups than in the placebo group. In Study B3461028, posthoc analyses of cardiac biomarker data prognostic of survival (NT-proBNP) and CV related hospitalizations (Troponin I) suggest differentiation between the 80 mg and 20 mg doses and an advantage of the 80 mg dose compared to 20 mg. Combined with

current analyses of the survival data of Study B3461045, B3461028's ongoing extension study, 80 mg tafamidis meglumine was recommended. To facilitate patient convenience, the sponsor has developed a single 61 mg tafamidis (as the free acid, PF-06291826) soft capsule, instead of 4 20 mg tafamidis meglumine soft gel capsules in order. A bioequivalence (BE) study, B3461056, was conducted and showed bioequivalence results between 80 mg tafamidis meglumine with 61 mg tafamidis. Details on justification for dose of 80 mg (4 x 20 mg) and development of its bioequivalent single capsule of 61 mg tafamidis is presented in Section 4.3. Pfizer considers 61 mg tafamidis once daily (bioequivalent to 80 mg [4 x 20 mg] tafamidis meglumine) as the recommended dose for patients with ATTR-CM.

The primary analysis used a hierarchical combination of all-cause mortality and frequency of CV-related hospitalizations (which is defined as the number of times a patient is hospitalized [ie, admitted to a hospital] for CV-related morbidity) over the duration of the trial, applying the method of Finkelstein-Schoenfeld.

A clinically relevant, statistically significant (p=0.0006) reduction of 30% in all-cause mortality and frequency of CV-related hospitalizations at 30 months was demonstrated for patients treated with tafamidis meglumine compared to those treated with placebo. This benefit was further reflected consistently and robustly in key secondary and exploratory analyses.

Study B3461028 enrolled 17 (of 441) participants in Japan (5 participants in the placebo group, 2 participants in the tafamidis meglumine 20 mg group, ten participants in the tafamidis meglumine 80 mg group). The sub-analysis of primary and key secondary endpoints data from these participants suggest no apparent trends that deviated from the overall test population.

A recent analysis of available survival data from Study B3461045, an ongoing, long-term extension study for participants previously enrolled in study B3461028, suggest a meaningful 10.2% reduction in risk of death (Hazard ratio 0.8976, 95% CI 0.5711, 1.4108) in patients on 80 mg compared to 20 mg of tafamidis meglumine over the longer period of treatment (p=0.6395). These results supported the dose recommendation of 80 mg tafamidis meglumine.

These points summarized the evidence supporting the expectation that the tafamidis meglumine clinical profile in the Chinese population will be consistent with the global population and is largely derived from experience with Japanese patients.

The safety profile of tafamidis meglumine for the treatment of ATTR-CM has been evaluated in 377 ATTR-CM patients in the pivotal Phase 3 Study B3461028 and its ongoing long-term extension (LTE) Study B3461045, as well as in the Phase 2 Study B3461025 and the associated ongoing LTE, Study B3461026 (data provided for both ongoing LTEs through cutoff date of 01 August 2018). Tafamidis safety data are also presented from 17 Phase 1 studies 348 healthy participants, as well as a Phase 1 study in participants with hepatic impairment. Additional supportive safety data are provided from 5 clinical studies (cutoff date 03 January 2017) involving ATTR-PN patients (n=137) and post-marketing data (cutoff

date 01 August 2018), as well as safety data from tafamidis-treated patients enrolled in Study B3461001 (Transthyretin-Associated Amyloidosis Outcomes Survey [THAOS]; cutoff date 01 August 2018).

Tafamidis treatment was generally safe and well tolerated in the study participant population, with an average age of 74, with few dose reductions and a similar frequency of TEAEs and serious TEAEs between the treatment groups. The majority of the AEs were mild or moderate in severity and discontinuation due to AEs, both permanent and temporary, were less common in the tafamidis groups than in the placebo group. No adverse drug reactions were identified with tafamidis administration in the ATTR-CM patient population.

2.3. Benefit/Risk Assessment

With tafamidis treatment, Chinese ATTR-CM patients will be expected to avoid TTR destabilization and thereby delay progression of ATTR-CM with well tolerated safety profile. Participants participating in the study may have the probability of experiencing the events listed in local product label.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of tafamidis may be found in the package insert, which is the single reference safety document (SRSD) for this study.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
• To characterize the safety profile of tafamidis once daily for the treatment of Chinese ATTR-CM patients in clinical practice.	• Not applicable.	• Incidence of treatment-emergent adverse events.
Secondary:		**Secondary:**
• To characterize the descriptive efficacy of tafamidis once daily in Chinese ATTR-CM patients. • To characterize tafamidis PD in Chinese ATTR-CM patients. • To characterize the impact on quality of life of tafamidis once daily for the treatment of Chinese ATTR-CM patients. • To characterize tafamidis PK in Chinese ATTR-CM patients.	• Not applicable.	• Assessment of 6-MWT, NT-pro BNP at scheduled visits. • TTR stabilization and TTR concentration at baseline (pre dosing) on Day 1, at Months 1, 6, and 12 (or End of Treatment (EOT)). • Kansas City Cardiomyopathy Questionnaire overall summary scores, EQ-5D-5L index scores and EQ-5D VAS scores, 12-Item Short Form Survey (SF-12) scores, at Day 1, Months 6, 12 (or End of Treatment (EOT)). • PK: plasma concentrations of tafamidis at Months 1, 6, and 12 (or EOT)).

4. STUDY DESIGN

4.1. Overall Design

This is a national, multi-center, single-arm study, open to patients with symptomatic ATTR-CM who are tafamidis naïve. This study is to obtain safety, description efficacy, PK and PD data following the approval of tafamidis 61 mg soft capsule orally once daily, with or without food. The potential site number will be 5-10 and at least 53 patients will be enrolled. The participants of greater than or equal to NYHA class III should not be more than 1/3 of all enrolled participants.

Patients will continue to receive their current medications and all other standard care for their disease based on clinical practice. The use of permitted concomitant medication must be in accordance with tafamidis package insert. Concomitant medication not permitted in this study is described in Section 6.5.

Total duration of study participation for each participant receiving tafamidis once daily with approved dose is 12 months. The following visit dates after baseline visit should be based on the date of the Baseline visit except the post-treatment follow-up.

Participants will complete protocol required tests and procedures as described in Schedule of activities. A final study report will be completed approximately 3 years after the date of the first tafamidis patient enrollment in the study.

Scheduled Visits: Day 1, Months 1, 3, 6, 9,12 (or End of Treatment), clinic visit at Day 1, Month 1, Month 6, Month 12, telephone contact at Month 3 and Month 9.

4.2. Scientific Rationale for Study Design

This study is to collect safety, descriptive efficacy PK, and PD data for tafamidis once daily with approved formulation. Incidence of treatment-emergent adverse events will be collected for primary endpoint analysis. Blood samples and special clinical assessments will be collected for secondary endpoints analysis, including 6-minutes walk test (6-MWT), N Terminal prohormone B type Natriuretic Peptide (NT-pro BNP), TTR stabilization, TTR concentration, plasma concentrations of tafamidis, Kansas City Cardiomyopathy Questionnaire Overall Score, EuroQoL 5 Dimensions 5 Levels (EQ-5D-5L) Index Score and EuroQoL 5 Dimensions visual analogue scale (EQ-5D VAS) scores, 12-short item survey form (SF-12) scores at each defined visit. To collect the PK data will know the drug exposure and safety of tafamidis in Chinese patients.

4.3. Justification for Dose

Based on results of Phase 3 pivotal study B3461028 and the bioequivalence Study B3461056, globally, the proposed clinical dosing regimen is 80 mg tafamidis meglumine orally (administered as 4 20 mg capsules, one capsule contains 12.2 mg tafamidis, the active pharmaceutical ingredient) once daily and/or tafamidis 61 mg (bioequivalent to the formulation/dosage of tafamidis meglumine 80 mg (4 x 20 mg)) orally once daily, with or without food.

The therapeutic indications in United States Prescribing Information are "Vyndaqel (tafamidis meglumine) and Vyndamax (tafamidis) indicated to reduce all cause mortality and cardiovascular related hospitalization in patients with wild type or hereditary transthyretin amyloid cardiomyopathy".

For China, in order to facilitate ATTR-CM patient convenience, the proposed and approved formulation and clinical dosing regimen is a tafamidis 61 mg soft capsule orally once daily, with or without food.

Rationale of 80 mg (4 x 20 mg) tafamidis meglumine soft capsules once daily

In pivotal Phase 3 study B3461028 protocol, tafamidis meglumine at 20 mg and 80 mg doses were employed and compared with placebo. The 20 mg dose of tafamidis meglumine had been used previously before B3461028 in both polyneuropathy and cardiomyopathy trials. A range of tafamidis meglumine exposures had been assessed in clinical pharmacology studies (Study Fx- 002, Study B3461040, and B3461031) in healthy volunteers that included the concentrations expected with an 80 mg dose. The addition of the 80 mg dose in B3461028, which was expected to result in near maximal TTR stabilization, would permit exploration of

a higher dose to assure that efficacy and safety had been explored across a range of adequately separated doses.

The results of pivotal Phase 3 study B3461028 demonstrated that comparable treatment effects were observed for the primary analyses (all-cause mortality and the frequency of cardiovascular-related hospitalizations) and secondary analyses (including TTR stabilization at Month 1) when analyzed by dose (20 mg and 80 mg). To further assess differences between tafamidis meglumine 20 mg and 80 mg doses to support dose recommendation, cardiac biomarker data by dose in Study B3461028 were explored and evaluated. Posthoc analyses of biomarker data prognostic of survival (NT-proBNP) and CV related hospitalizations (Troponin I) suggest differentiation between the 80 mg and 20 mg doses and an advantage of the 80 mg dose compared to 20 mg. In addition, this study enrolled 17 (of 441) participants in Japan (5 participants in the placebo group, 2 participants in the tafamidis meglumine 20 mg group, ten participants in the tafamidis meglumine 80 mg group) and a sub-population report was generated. Although the sample size is limited, efficacy and safety results in the Japanese participants were consistent with the results from the overall study population.

Upon completion of the Month 30 visit in Study B3461028, patients were to be eligible for treatment with tafamidis in a separate ongoing extension study (B3461045), which would permit the collection of additional safety and efficacy data, and would include the assessment of hospitalizations, mortality, and other outcomes relating to disease progression. For the purpose of this study, 30 months was defined as 910 days. Eligibility for the extension study (B3461045) required patient participation in Study B3461028 at least through Day 896 (Month 30 minus 2 weeks). Results from B3461045 continue to demonstrate a significant reduction in all-cause mortality. Current analyses of the survival data from the ongoing Study B3461045 indicated a marginal yet meaningful 10.2% reduction in risk of death in patients on 80 mg compared to 20 mg of tafamidis meglumine over the longer period of treatment.

Development and rationale of a single 61 mg tafamidis soft capsule, bioequivalent to 4 20 mg tafamidis meglumine capsules at steady state

In order to facilitate patient convenience, the sponsor has developed a formulation, a single 61 mg tafamidis soft capsule, that provided patients with a single oral dosage form instead of 4 20 mg tafamidis meglumine soft gel capsules. A single 80 mg tafamidis meglumine soft gel capsule is technically not feasible because of a concentration-dependent gelling of tafamidis meglumine. Multiple CCI forms were screened and it was determined that tafamidis was the favored active pharmaceutical ingredient.

Study B3461056 was an open label, randomized, 2-period, 2-sequence, crossover, multiple dose pivotal bioequivalence study in fasted healthy volunteers comparing area under the concentration-time curve over the dosing interval tau (AUC_{tau}), and maximum observed drug concentration (C_{max}) at steady-state, of 61 mg tafamidis soft capsules (Treatment A, Test) and 4 × 20 mg commercial tafamidis meglumine soft capsules (Treatment B, Reference). Bioequivalence criteria were met for the tafamidis 61 mg capsule relative to the tafamidis

meglumine 4 × 20 mg capsules after repeated oral daily dosing for 7 days (on study Days 1 and 2, a second dose of the study medication was administered approximately 12 hours after the first dose and at least after a 2 hour fast). The ratio of adjusted geometric means (90% CI) of tafamidis AUC_{tau} and C_{max} were 102.28% (97.99%, 106.76%) and 94.12% (89.09%, 99.42%) respectively, following administration of the tafamidis 61 mg capsule relative to tafamidis meglumine 4 × 20 mg capsules. The corresponding 90% CIs were contained within the (80%, 125%) bioequivalence acceptance range.

Study B3461054 assessed effect of food with the 61 mg tafamidis soft capsule formulation. Based on the ratios of adjusted geometric means, tafamidis (area under the concentration-time curve from time 0 to infinity (AUC_{inf}) and C_{max} following a single dose increased by approximately 6% and 32% respectively, for the 61 mg tafamidis capsule fed vs. fasted. Given that tafamidis is administered as a chronic medication and that overall exposure was not different between the fed and fasted treatment, these data support dosing without regard to food. In addition, simulations using the population PK model suggest the difference in steady-state C_{max} under fed conditions is approximately 2% compared to fasted conditions, which is considered not to be clinically meaningful.

Hence, this study will employ tafamidis at 61 mg, orally once daily, the approved dose regimen.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including Month 12 or Early Study Discontinuation.

The end of the study is defined as the date all participants have completed the visits scheduled in the SoA.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

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

5.1. Inclusion Criteria

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

Age and Sex:

Male and female participants, age greater than or equal to 18 at screening visit.

Type of Participant and Disease Characteristics:

Participants, in the opinion of the investigator, who are willing and able to take tafamidis and comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Participant has documented ATTR-CM, which is defined as:

a. Variant ATTR-CM:

- presence of a variant TTR genotype associated with cardiomyopathy and presenting with a cardiomyopathy phenotype (eg, a history of congestive heart failure);
- evidence of cardiac involvement by echocardiography with an end diastolic interventricular septal wall thickness >12 mm;
- presence of amyloid in biopsy tissue, such as fat aspirate, salivary gland, median nerve connective tissue sheath, or cardiac (amyloid demonstrated per appropriate stain such as Congo red or alcin blue stain) OR radionuclide bone scintigraphy (99mTc-PYP) Scintigraphy.

b. Wild-type ATTR-CM:

- absence of a variant TTR genotype;
- evidence of cardiac involvement by echocardiography with an end diastolic interventricular septal wall thickness >12 mm;
- presence of amyloid deposits in biopsy tissue, such as fat aspirate, salivary gland, median nerve connective tissue sheath, or cardiac (amyloid demonstrated per appropriate stain such as Congo red or alcin blue stain), with TTR precursor protein identification by either immunohistochemistry, mass spectrometry OR radionuclide bone scintigraphy (99mTc-PYP).

Weight: Not applicable.

Informed Consent:

Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent document (ICD) and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions:

1. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or study intervention administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

Prior/Concomitant Therapy:

2. Participants who have prior liver and/or heart transplant.

3. Participants with primary (light chain) or secondary amyloidosis.

Prior/Concurrent Clinical Study Experience:

4. Previous administration with an investigational drug or vaccine within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

Other Exclusions:

5. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or Pfizer employees, including their family members, directly involved in the conduct of the study.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4 Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the schedule of activities (SoA), the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who recover from acute medical conditions may, according to the best medical judgment of the investigator, be appropriate for rescreening.

If individuals recovered within 45 days, the individual inclusion/exclusion criteria may not need a repeat procedure to rescreen. It may be necessary to obtain informed consent again for some participants but not others based upon the study design, the medical condition, or the age and other participant issues. Institutional review boards (IRBs)/ ethics committees (ECs) may also have specific guidances for their sites

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, the term investigational product may be used synonymously with study intervention. Investigators will confirm the eligibility of each participant to meet inclusion/exclusion criteria. Participant eligibility for participation in the study will receive tafamidis 61 mg (the approved dose) orally once daily with or without food, for 12 months following the assessment as the screening and baseline visits.

6.1. Study Intervention(s) Administered

Intervention Name	Tafamidis free acid
ARM Name	Treatment
Type	Interventional type: Drug
Dose Formulation	In accordance with China authority approved package insert
Unit Dose Strength(s)	Milligram
Dosage Level(s)	61 mg, once daily
Route of Administration	Oral
Investigational Medicinal Product (IMP) and Noninvestigational Medicinal Product (NIMP)	IMP
Sourcing	Provided centrally by the sponsor from China authority approved package insert.
Packaging and Labeling	Study intervention will be provided with approved package. Refer to Section 6.3.1 for investigational product allocation.
[Current/Former Name(s) or Alias(es)]	Tafamidis

Study intervention will be dispensed at baseline (Day 1), Month 1 and Month 6 visits. Participants will be instructed to take the medication on a daily basis. They will also be instructed to bring all of their study medication back to the study site, including used and unused study medication, at each scheduled study visit so that the total amount of drug taken can be determined and unused medication collected by site personnel. Study intervention count will be performed at each scheduled visit for all participants.

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

In the event that participants experience adverse events that may be associated with the tolerability of treatment with tafamidis that may impact dosing adherence, they should return to the clinic with their medication. If the investigator assesses that the tolerability issue is persistent and anticipated to impact dosing adherence and that the participant's safety is not

compromised by continuing treatment, the site has the option to discontinue dosing for this participant and to terminate study participation.

Patients will continuously receive their current medications and all other standard care for their disease. The use of permitted concomitant medication must be in accordance with tafamidis label.

6.1.1. Administration

Participants will swallow the investigational product whole, and will not manipulate or chew the investigational product prior to swallowing and taking the capsules with a glass of water. Participants will be instructed to dose at a consistent time of day. Participants will be instructed to start taking their medication each day in the morning (AM dosing); however, it is permitted for participants to take his/her medication in the afternoon or evening prior to a clinic visit (eg, the Month 6 visit) when the timing of PK sample collection is prohibitive for adherence with AM dosing. Participants should not take an extra dose of medication in the event that a dose from a previous day is missed and should resume dosing capsules per day from an individual row on the study medication at the next planned dosing time. Similarly, if multiple doses are missed in succession, the participant should resume dosing at the next planned dosing time without taking additional doses to make up for those doses that were missed. Instructions on dosing are provided on the Participant Daily Dosing Diary.

At the end of each visit, sites will instruct participants, in writing on the front of the Participant Daily Dosing Diary, when to take their medication prior to their next study visit. This is especially important if the next visit has a collection of blood sample(s) for PK analysis.

Knowing the actual time of dosing is essential for appropriate analysis of samples for TTR stabilization, TTR concentration, and for tafamidis pharmacokinetic measurements. On the day of the study visit, participants will write the actual time that they took their medication in the Participant Daily Dosing Diary and the site staff will record this dosing time in the case report form (CRF).

On Day 1 (Baseline Visit), participants will be instructed to take their first daily dose of 61 mg tafamidis, after the completion of the baseline procedures and to continue dosing capsules each day in the morning (AM dosing) until the next study visit of Month 1 visit. At the end of the clinic visit, the participants will be reminded to take their medication in the clinic, rather than at home, on the day of the next visit of Month 1, as indicated on the Participant Daily Dosing Diary.

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

study site personnel. Study site personnel will also record in the CRF the time of dosing on the day before the Month 1 visit as reported by the participant.

During Month 3 visit (Telephone visit), schedule the next appointment and participant will be instructed to take their medication **at home** prior to the next clinic visit as indicated on the Participant Daily Dosing Diary. Visit scheduling and dosing time instructions for participants must consider that the tafamidis concentration sample is to be collected 7 hours (±2.5 hours) after dosing. It should be noted that the participants are permitted to take the medication prior to the Month 6 visit in the afternoon or evening on the day prior to Month 6 visit if necessary to adhere to the PK sampling schedule. Participants will be instructed to accurately record on the Participant Daily Dosing Diary the actual time at which they took their prior 2 doses of medication taken at home prior to the Month 6 visit. The participant will be reminded to return to the clinic with all dispensed study medication.

For Month 6 visit, it should be noted that dosing should take place 7 hours (±2.5 hours) prior to the timing of PK sample. On the day prior to Month 6 visit, participants are permitted to take their usual AM dose and then take the next day's dose in the afternoon or evening if necessary to adhere to the PK sampling schedule. Participants will take their scheduled dose at home prior to the clinic visit (either in afternoon or evening of the day prior to this visit day, or in AM of this visit day) and record the actual time of dosing on their Participant Subject Daily Dosing Diary. Study site personnel will record in the CRF the time of the prior 2 doses of medication taken at home prior to the Month 6 visit as reported by the participant on their Participant Daily Dosing Diary.

During Month 9 visit (Telephone visit), schedule the next appointment and participant will be instructed to take their medication in the clinic, rather than at home, on the day of the next visit of Month 12. A Participant Daily Dosing Diary stating the date and time of the next visit of Month 12 will be issued to the participant. Participants will be instructed to accurately record on the Participant Daily Dosing Diary the actual time at which they took their dose of medication at home on the day before the Month 12 visit orEnd of Treatment visit. The participant will be reminded to return to the clinic with all dispensed study medication.

On the day of the Month 12 study visit, participants will **NOT** take their study medication at home prior to the Month 12 clinic visit. Study medication on the day of the Month 12 visit will be taken in the clinic in order to accurately and conveniently time the tafamidis concentration blood sample, which is to be 1 hour (±30 minutes) after the actual time of dosing. The actual time of dosing will be recorded by the study site personnel. Study site personnel will record in the CRF the time of dosing on the day before the Month 12 visit as recorded by the participant on their Participant Daily Dosing Diary.

In the event that participants experience adverse events that may be associated with the tolerability of treatment with tafamidis that may impact dosing adherence, they should return to the clinic with their medication. If the investigator assesses that the tolerability issue is persistent and anticipated to impact dosing adherence and that the participant's safety is not

compromised by continuing treatment, the site has the option to discontinue dosing for this participant and to terminate study participation.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention, as applicable for temperature-monitored shipments.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperature since previously documented for all site storage locations upon return to business.

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). All study interventions will be accounted for using an investigational product accountability form/record. At each scheduled clinic visits starting at Month 1; participants will bring their study medication with them to the site. The investigator's site must maintain adequate records documenting the receipt, use, loss, or other disposition of the drug supplies as outlined in the monitoring plan.

4. Further guidance and information for the final disposition of unused study interventions are provided in the package insert.

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

6. Study interventions should be stored in their original containers and in accordance with the labels.

7. Site staff will instruct participants on the proper storage requirements for take-home study intervention.

8. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. It will not be considered a protocol deviation if Pfizer

approves the use of the study intervention after the temperature excursion. Use of the study intervention prior to Pfizer approval will be considered a protocol deviation. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the package insert.

9. The sponsor or designee will provide guidance on the destruction of unused study intervention (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

6.2.1. Preparation and Dispensing

See the package insert for instructions on how to prepare the investigational product for administration. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Investigational Product

This is a single-arm study. Participant eligibility for participation in the study will receive tafamidis 61 mg, the approved dose in China, once daily for 12 months following the assessments at the screening and baseline visits.

There is no requirement of blinding and randomization.

6.4. Study Intervention Compliance

Participants will be instructed to take the medication on a daily basis. They will also be instructed to bring all of their study medication back to the study site, including used and unused study medication, at each scheduled study visit so that the total amount of drug taken can be determined and unused medication collected by site personnel.

Participant compliance with investigational product will be assessed at each visit. Compliance will be assessed by counting returned capsules. Participants will be considered to be adherent to the dosing requirements of the study if they have taken study medication per day on at least 80% of the days of study participation. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF. Participants with less than 80% dosing adherence will be excluded from the per protocol analysis set.

All doses of investigational product will be administered by the appropriately designated study staff at the investigator site.

6.5. Concomitant Therapy

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

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

Participants may use supplements and medications during the course of the study with the exception of those listed in package insert. Medication considered to be standard of care are permitted but should be recorded on the CRF. If a participant is offered, in accordance with the prevailing local guidelines, a COVID-19 vaccine, it should be permitted. This would be recorded as a concomitant medication and standard AE collection and reporting processes would be followed.

Prohibited Therapies:

1. Use of non-steroidal anti-inflammatory drugs (NSAIDs) other than those noted below is prohibited. Some NSAIDs, like diflunisal, can bind to the thyroxine binding sites on transthyretin. Chronic use (greater than 4 times/month) of NSAIDs before the study is prohibited except the following permitted NSAIDs: acetylsalicylic acid, etodolac, ibuprofen, indomethacin, ketoprofen, nabumetone, naproxen, nimesulide, piroxicam, and sulindac. Topical ophthalmic NSAIDs administered while the patient's nasal punctum is occluded are also permitted.

2. Use of any investigational drug or vaccine during the study is prohibited.

3. Additionally, the use of diflunisal, tauroursodeoxycholate and doxycycline or any other TTR stabilizing agent or experimental interventions for transthyretin amyloid cardiomyopathy within 30 days prior to the study entry and/or during study participation is not permitted.

4. Digitalis and calcium channel blockers (eg, verapamil, diltiazem) are prohibited concomitant medications because they bind to amyloid fibrils and may lead to increased toxicity.

5. Use of any dosage form of tafamidis before the study is prohibited.

Contraindicated therapies must be in accordance with investigational drug package insert.

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are women of childbearing potential (WOCBP) (see Appendix 4).

Use of traditional Chinese medicine should obtain the permission of investigator.

6.5.1. Rescue Medicine

There is no rescue therapy to reverse the adverse events (AEs) observed with tafamidis; standard medical supportive care must be provided to manage the AEs.

6.6. Dose Modification

Not applicable.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study. Participants should refer to routine clinical care procedure with consulting from clinical physicians after end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Participants with one or more of the following criteria in the study duration will discontinue the investigational drug:

- Experience adverse events that may be associated with the tolerability of treatment with tafamidis, other safety criteria(eg, AE, PK criteria), disease state criteria (eg, progressive disease), etc. The site has the option to discontinue dosing for this participant and to terminate the participant's study participation.

Note that discontinuation of study intervention does not represent withdrawal from the study unless the patient requests withdrawal from the study. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for the End of Treatment visit (within 2 weeks after the End of Treatment date). See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed. In the event of early Study Intervention Discontinuation, the site staff will follow-up on the participant's vital status at Month 12 from baseline (or at Early Study Discontinuation visit for a participant who withdraws consent for any further contact).

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

ECG Changes

A participant who meets either bulleted criterion based on electrocardiogram (ECG) readings will be withdrawn from the study.

QTcF >500 msec.

Change from baseline: QTc >60 msec.

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

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1. Temporary Discontinuation

Not applicable.

7.1.2. Rechallenge

Not applicable.

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;

Participants should be questioned regarding their reason for withdrawal. The participant will be permanently discontinued both from the investigational product and from the study at that time.If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations 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.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow-up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

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

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

Where multiple procedures are scheduled at the same nominal time point(s) relative to dosing, the following chronology of events is suggested:

1. ECG

2. Vitals: Blood pressure/pulse rate

3. Blood sample collection

4. Blood specimens for plasma concentrations of tafamidis, TTR stabilization, and TTR concentrations should be obtained within the specified time windows if applicable.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue investigational product.

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

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICD may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

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

Additionally, visits should be completed as close to the scheduled timeframe as possible but not to exceed 1 week of the target date for each scheduled visit. The duration of this study is 12 months. Follow-up visit dates should be based on the date of the Baseline visit, not the date of the previous follow-up visit except the post-treatment follow-up.

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

The total planned per protocol blood sampling volume for individual participants in this study is approximately 280 mL, including potential additional blood samples taken for safety assessments at times specified by investigator. Additional blood samples may be taken for safety assessments when required for management of adverse events, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days.In exceptional circumstances, such as medical emergencies, this volume may be exceeded and will not constitute a protocol deviation in such circumstances.

8.1. Efficacy Assessments

6-Minute Walk Test (6-MWT)

A 6-MWT will be conducted at time points in the SoA. The test will be conducted in accordance with guidelines established by the American Thoracic Society.

New York Heart Association Classification

Participants will be evaluated using the New York Heart Association (NYHA) classification at time points in the SoA. For NYHA classifications refer to Appendix 8.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

8.2.1. Physical Examinations

A full physical examination should include all of the following assessment.

Height and weight will also be measured and recorded.

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

A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen) and are to be performed at all other study visits.

Weight will also be measured and recorded.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

Vital signs will be recorded at each study visit.

Vital signs will be measured with the participant in a semisupine position after at least 5 minutes of rest and will include body temperature, systolic and diastolic blood pressure, and pulse rate and respiratory rate. Three readings of blood pressure and pulse rate will be taken. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded in the CRF.

8.2.3. Electrocardiograms

12-Lead ECGs should be collected at times specified in the SoA using an ECG machine that automatically calculates the heart rate and measures PR interval (PR), QT interval (QT), and corrected QT (QTc) intervals and QRS complex (QRS). All scheduled ECGs should be performed before blood pressure or pulse measurements or blood collection, For ECG recordings, the participants will remain supine for about 5 minutes before recording the ECG.

If a postdose QTcF interval remains ≥60 msec from the baseline **and** is >450 msec; or b) an absolute QTcF value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator), or QTc intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than the criterion listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

ECG data will be submitted to a site laboratory for measurement. The final ECG report from the central laboratory should be maintained in the participant's source documentation and be the final interpretation of the ECG recording. Any clinically significant changes from the

baseline/Day 1 ECG may potentially be AEs (Appendix 7) and should be evaluated further, as clinically warranted.

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

ECG values of potential clinical concern are listed in Appendix 7.

8.2.4. Echocardiograms

Echocardiography (2D Doppler) will be performed for all participants at times specified in the SoA. The assessment of end-diastolic interventricular septal thickness for study entry will be based on the echocardiogram performed at the Screening visit as interpreted by the independent central laboratory. If the Screening echocardiographic recording is not clear enough to accurately determine the end-diastolic interventricular septal wall thickness, it must be repeated. Each echocardiogram will be recorded and reviewed locally by the clinical site, and the clinical significance of echocardiogram findings will be assessed by the Investigator. Each echocardiogram will also be sent to an independent central laboratory that will conduct a centralized review of the results. The central reading of the Screening echocardiogram must be completed prior to participant randomization at the Baseline visit.

The following parameters will be included in the assessment:

1. End-diastolic interventricular septal wall thickness (mm).

Left ventricle posterior wall thickness (mm).

Left ventricular ejection fraction (%).

Left ventricular stroke volume (mL).

Fractional shortening (%).

Left atrial diameter, anterior-posterior (mm).

Left ventricular end systolic diameter (mm).

Left ventricular end systolic volume (mL).

Left ventricular end-diastolic diameter (mm).

Left ventricular end-diastolic volume (mL).

Left ventricular mass (g).

The ratio of peak velocity blood flow from gravity in early diastole (the E wave) to peak velocity flow in late diastole caused by atrial contraction (the A wave) (E/A).

8.2.5. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in

Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.6. Body Mass Index/Modified Body Mass Index.

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

8.2.7. Hospitalization Determination

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

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

Hospitalization does not include admission to the following:

1. Rehabilitation facilities.

Hospice facilities.

Respite care (eg, caregiver relief).

Skilled nursing facilities.

Nursing homes.

Routine emergency room admissions (less than 24 hours).

Same-day surgeries (as outpatient/same-day/ambulatory procedures).

8.2.8. Pregnancy Testing

Pregnancy tests should be serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. A negative pregnancy test result will be required prior the participant's receiving the tafamidis. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant legally authorized representative will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 28 calendar days, except as indicated below after the last administration of the study intervention.

Follow up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion.

- A male family member or healthcare provider who has been exposed to the study intervention by ingestion then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 calendar days after last administration of the study intervention.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

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

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;

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

Additional information regarding the EDP may be requested by the sponsor. 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 participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

The Tafamidis Enhanced Surveillance Pregnancy Outcomes (TESPO) program follows the progress and outcome of reported pregnancies in women exposed to tafamidis. Tafamidis exposure during pregnancy will be reported to TESPO program.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the CT SAE Report Form. Since the information does not pertain to a

participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events

Not applicable. Cardiovascular and death events will be collected as AE/SAE even though these events are manifestations of the end stage of TTR-CM.

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

Lack of efficacy in an approved indication should be reported as an SAE to Pfizer Safety.

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.9.1. Time Period for Detecting Medical Device Deficiencies

Not applicable.

8.3.9.2. Follow up of Medical Device Deficiencies

Not applicable.

8.3.9.3. Prompt Reporting of Device Deficiencies to Sponsor

Not applicable.

8.3.9.4. Regulatory Reporting Requirements for Device Deficiencies

Not applicable.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of tafamidis greater than daily dose of study intervention within a 24-hour time period will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose and may be used in case of doverdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of tafamidis. Closely monitor the participant for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE**.

5. Obtain a blood sample for PK analysis within 14 days from the date of the last dose of study intervention if requested by the medical monitor (determined on a casebycase basis).

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Blood samples of approximately 3 mL, to provide an approximately 1 mL plasma, will be collected into appropriately labeled tubes containing dipotassium ethylenediaminetetraacetic acid (K2EDTA) for measurement of plasma concentrations of tafamidis as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the PK of tafamidis. Samples collected for analyses of tafamidis plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method.

Genetic analyses will not be performed on these plasma samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.

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

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

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.6. Pharmacodynamics

Pharmacodynamic (PD) parameters will be evaluated in this study.

TTR Stabilization and TTR Concentration Measurements

One (1) dipotassium ethylenediaminetetraacetic acid (K2 EDTA) blood sample of approximate 10 mL (with exception of an additional approximate 10 mL of the pre-dose blood sample only on Day 1 for method development and validation) will be collected as specified in the SoA for measurement of TTR stabilization and TTR concentration. The actual date and time (24-hour clock time) of each sample will be recorded. Samples will be analyzed using validated analytical methods in compliance with Pfizer standard operating procedures. Detailed instructions for collection, storage, labeling, and shipment of all samples are provided in a separate study laboratory manual.

As part of understanding the PD of the study intervention, samples may be used for evaluation of the bioanalytical method. These data will not be included in the Clinical Study Report (CSR).

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

8.7. Genetics

Genetics information will be collected in the study.

8.7.1. Specified Genetics

Blood samples of approximately 3 ml will be collected for measurement of genotyping for mutation of TTR gene at screening period for each participant.

8.7.2. Banked Biospecimens for Genetics

Not applicable.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.8.1. Specified Gene Expression (RNA) Research

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

8.8.2. Specified Protein Research

Specified protein research is not included in this study.

8.8.3. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.9. Health Economics

Health Economics parameters will be evaluated in this study as Patient Reported Outcomes:

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

Kansas City Cardiomyopathy Questionnaire

The Kansas City Cardiomyopathy Questionnaire (KCCQ) (Section 10.9.1) (Green 2000)[8] is a 23-item subject-completed questionnaire that assesses health status and health-related quality of life in participants with heart failure. Items assess the ability to perform activities of daily living, frequency and severity of symptoms, the impact of these symptoms, and health-related quality of life. Response options vary by question. Scoring yields scores for 6 domains (Physical limitation, Symptom stability, Symptoms, Self-efficacy, Social limitation, and Quality of life), domain summary scores (Functional summary and Clinical summary), as well as an Overall Summary score. Domain scores are transformed to a 0 to 100 range; higher scores indicate better health status. It takes approximately 4-6 minutes for a participant to complete the KCCQ. Participants will complete the KCCQ at the times listed in the Schedule of Activities. In each instance of administration, the KCCQ should be completed by participants before completing the EQ-5D-5L (Section 10.9.2) and SF-12 (Section 10.9.3). The KCCQ can be found in Section 10.9.1

EuroQoL 5 Dimensions 5 Levels (EQ-5D-5L)

The EQ-5D-5L (5 levels version) is a brief, self-administered generic health status instrument that takes about 5 minutes to complete.[9] The instrument consists of 2 parts. In the first part, respondents are asked to rate their current health state on 5 dimensions (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) with each dimension having 3 levels of function (1=no problem, 2=some problem, and 3=extreme problem). The second part is a participant's self-rating of current health state on a Visual Analog Scale (EQ-5D VAS) with endpoints labeled 'best imaginable health state' (score of 100) and 'worst imaginable health state' (score of 0). The scores from the 5 dimensions may be used to calculate a single index value, also known as a utility score. Participants will complete the EQ-5D-5L (Section 10.9.2) at the times listed in the Schedule of Activities.

Participants should complete the EQ-5D-5L after the KCCQ (Section 10.9.1). The EQ-5D-5L can be found in (Section 10.9.2).

12- item short form health survey (SF-12)

A patient's overall quality of life, as measured by the 12-Item Short Form Survey (SF-12), will be assessed at the times listed in the SoA. This questionnaire should be completed by the patient after the KCCQ and EQ-5D-5L, and prior to other required visit assessments. SF-12 is developed as a shorter alternative to the SF-36 for use in large-scale studies, and its reliability and validity have been documented. It is an instrument with different weights for scoring physical and mental health, and measures health-related quality of life with 12 items

categorized in eight areas: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health.

A sample of the SF-12 is provided in Section 10.9.3.

8.10. Biopsy Documentation of Amyloid

In the event that there is no documentation of prior biopsy or radionuclide bone scintigraphy (99mTc-PYP) and demonstration of TTR amyloid deposition by either mass spectrometry, immunohistochemistry or scintigraphy, cardiac or non-cardiac tissue will be biopsied and tested by the investigational site as per the site's standard of care and evaluated with Congo red stain or other analysis can be utilized to confirm the deposit of amyloid. Stained tissue will be viewed under polarized light used to demonstrate amyloid characteristic 'apple-green' birefringence. For participants without identification of a TTR variant and demonstration of amyloid deposition who may have a diagnosis of wild-type ATTR-CM, analysis will be performed to confirm the precursor protein basis for amyloid deposition, by either: mass spectrometry or immunohistochemistry.

For purposes of this study, an existing biopsy result will be considered valid if it is documented in writing and the biopsy was performed within 5 years of study enrollment. If the biopsy is not valid, it will be repeated as a screening procedure at the investigational site.

9. STATISTICAL CONSIDERATIONS

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

9.1. Estimands and Statistical Hypotheses

This is an estimation study with no statistical hypothesis to test.

9.2. Sample Size Determination

In order to attain an 80% probability of observing at least 1 participant having an event for TEAEs with incidence rate of 3%, at least 53 participants need to be treated.

9.3. Populations for Analysis

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICD
Efficacy	All participants who take at least 1 dose of tafamidis
Safety	All participants who take at least 1 dose of tafamidis

Population	Description
Pharmacokinetic (PK)	All participants who have at least 1 quantifiable plasma tafamidis concentration
Pharmacodynamic (PD)	All participants who have at least 1 data of the TTR stabilization

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

Unless otherwise stated, descriptive analyses will be done for overall and by NYHA baseline classification. Baseline for any endpoints is defined as the last measurement prior to dosing on Day 1 of the study. Change from baseline value is calculated by subtracting the baseline value from each follow up visit value.

9.4.1. Safety Analyses

All safety analyses will be performed on the safety population.

9.4.1.1. Treatment Emergent Adverse Event

All adverse events that start after the first dosing but before the last dose plus the lag time are treatment emergent adverse events. Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

The incidence of treatment-emergent adverse events will be tabulated by system organ class. The incidence of treatment-emergent adverse events will be displayed by severity and attribution. In addition, the incidence of serious adverse events and adverse events that cause withdrawal will be tabulated. All adverse events will be listed.

9.4.1.2. Electrocardiogram Analyses

Centrally over-read ECG variables will be summarized by mean change from baseline to each measurement time for heart rate, PR interval, QRS width, QT interval, and QTcF (Fridericia's correction) values.

Additionally, the incidence of categorical increases in QTc intervals will be provided. Categories for QTcF are ≥450 msec, ≥480 msec, and ≥500 msec. Categories for QTcF as change from baseline are: ≥30 msec increase, ≥60 msec increase. QTcF is considered the primary QTc value as this correction is anticipated to be more appropriate.

9.4.1.3. Body Mass Index/Modified Body Mass Index

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

9.4.1.4. Other Safety Assessments

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

All vital sign measurements will be displayed in listings by participant for each sample collection date and time with changes from baseline values included.

9.4.2. Pharmacodynamics Analyses: TTR Concentration and TTR Stabilization

The TTR concentration and percent TTR stabilization will be determined.--Declaring a participant to have been "stabilized" is defined as percent stabilization is equal to or more than 32%.

All pharmacodynamic analyses will be performed on the PD population. TTR concentration and percent stabilization will be summarized descriptively as continuous measures, by visit, for overall, by TTR genotype, and by NYHA baseline classification. The proportion of participants who achieve TTR stabilization (ie, who has been stabilized) and its 95% confidence interval will be calculated and summarized, as categorical measure, at each post-baseline time point, for overall, by TTR genotype, and by NYHA baseline classification.

9.4.3. Analyses for Efficacy Endpoints

All efficacy analyses will be performed on the efficacy population. For both baseline and change from baseline efficacy measures, descriptive statistics will be provided for each time point.

9.4.3.1. NT-Pro BNP

Plasma amino-terminal pro-B-type natriuretic peptide (NT-proBNP) is a guideline-mandated biomarker in heart failure. Used as an inclusion criterion for therapeutic trials, NT-proBNP enriches trial populations and is a valid surrogate endpoint. NT-proBNP offers prognostic information independent of standard clinical predictors and refines risk stratification.

9.4.3.2. TnI

Cardiac troponin T (cTnT) and cardiac troponin I (cTnI) were recognized as markers of myocardial damage, Troponin T or troponin I or both may be chronically elevated in cardiac amyloidosis. Cardiac troponin I is thought to be more accurate in assessment of myocardial damage. In the appropriate clinical context of a thickened ventricle and heart failure, an elevated troponin value (outside of an acute coronary syndrome) should trigger suspicion for cardiac amyloidosis.

9.4.3.3. 6 Minute Walk

Six-minute walking test is a kind of exercise test for patients with moderate to severe cardiopulmonary disease. The 6-MWT measures the longest distance a patient can walk on a straight course in 6 minutes.

9.4.3.4. New York Heart Association Classification

The New York Heart Association functional classification (NYHA class) is used to describe the functional capacity of adults with congenital heart disease to describe the severity of symptoms and exercise intolerance. An increase or decrease in NYHA classification relative to baseline will be summarized using a shift table at each time point post-baseline.

9.4.4. Quality of Life Analyses

Quality of life analyses will be performed on the efficacy population. Both baseline and change from baseline measures will be summarized descriptively by visit.

9.4.4.1. Kansas City Cardiomyopathy Questionnaire Overall Score

The KCCQ overall score assess the ability to perform activities of daily living, frequency and severity of symptoms, the impact of these symptoms, and health-related quality of life. Response options vary by question. Change from baseline in Kansas City Cardiomyopathy Questionnaire: (KCCQ) domain scores (Physical limitation, Symptom stability, Symptoms, Self-efficacy, Social limitation, and Quality of life) and domain summary scores (Functional summary and Clinical summary) will be evaluated.

9.4.4.2. EQ-5D-5L

The EQ-5D-5L essentially consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS).

The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the 5 dimensions can be combined into a 5-digit number that describes the patient's health state. The EQ-5D utility scores were calculated based on the available Chinese value set for the EQ-5D-5L instrument. The score ranges from -0.391 to 1, where 1 represents full health, 0 represents death, and a score less than 0 represents a health status worse than death.The EQ VAS records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The VAS scores can be used as a quantitative measure of overall self-rated health status that ranged from 0 (worst health) to 100 (best health).

Change from baseline in EQ-5D-5L: the EQ-5D-5L scores and EQ VAS scores will be evaluated.

9.4.4.3. 12-Item Short Form Survey (SF-12)

The 12-item Short Form Scale scores are estimated for 4 of the health concepts (physical function (PF), role physical (RP), role emotional (RE) , and mental health (MH) using two items each, whereas the remaining 4 (bodily pain (BP), general health (GH), vitality (VT), social function (SF) are represented by a single item. The raw scores of each item are coded, weighted, and summed into 2 scales: physical component summary score (PCS) and mental component summary score (MCS). Higher scores indicate better quality of life. Change from baseline in 12 Item-Survey Form (SF-12) Score: the Physical Component Summary(PCS), the Mental Component Summary (MCS) and overall scores (Physical Component Summary and Mental Component Summary) will be evaluated.

9.4.5. Pharmacokinetic Data

Pre-dose and post-dose plasma concentrations of tafamidis at scheduled visit will be summarized descriptively.

9.5. Interim Analyses

No formal interim analysis will be conducted for this study. As this is an openlabel/-sponsor-open study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating doseescalation- decisions, facilitating PK/PD modeling, and/or supporting clinical development.

9.5.1. Data Monitoring Committee

This study will not use a data monitoring committee (DMC).

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines;
- Applicable laws and regulations, including applicable privacy laws.

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

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

The investigator will be responsible for the following:

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

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

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

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and

of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/EC or study center.

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

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

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

The investigator further must ensure that each study participant or his/her legally authorized representative is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

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

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICD if the rescreening does not exceed 45 days from the previous ICD signature date.

If the exploratory research will be conducted, the ICD will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.4. Data Protection

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

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

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

10.1.5. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. US Basic Results are generally submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

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

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the European Medicines Agency (EMA) website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

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

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

10.1.6. Data Quality Assurance

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

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

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic form and are password protected to prevent access by unauthorized third parties.

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

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

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

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

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

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

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

10.1.7. Source Documents

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

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

Definition of what constitutes source data can be found in the hospital's participant chart or HIS system.

10.1.8. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;

Inadequate recruitment of participants by the investigator;

Discontinuation of further investigational product development.

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

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. Sponsor's Qualified Medical Personnel

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

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

Table 1. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Dipstick Urinalysis	Other
White blood cell count Hemoglobin Red blood cell count Neutrophils Lymphocytes Hematocrit Mean corpuscular volume Monocytes Mean corpuscular hemoglobin Eosinophils Mean corpuscular hemoglobin concentration Basophils Platelets	Sodium Inorganic Phosphorus Aspartate aminotransferase (AST) Potassium Glucose Gamma glutamyl transferase Chloride Total bilirubin Cholesterol Total protein Uric acid Blood Urea Nitrogen Albumin Thyroid-stimulating hormone Creatinine Globulin Total thyroxine (T4) Calcium Alanine aminotransferase (ALT) Free T4 Retinol binding protein Alkaline Phosphatase	pH Blood (free Hb) Ketones Glucose Bilirubin Protein Nitrite Specific gravity Urobilinogen	NT-pro BNP TnI International normalized ratio (INR) Prothrombin time (PT) Activated partial thromboplastin time (APTT) Fibrinogen (FIB) Hepatitis B surface antigen Hepatitis C antibody Human immunodeficiency virus antibody Syphilis antibody (anti-TP)

Investigators must document their review of each laboratory safety report.

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

10.3.1. Definition of AE

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

Events Meeting the AE Definition

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

The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE and meet the requirements as per Section 8.3.8.1. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE.

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

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or

outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

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

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

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the

exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

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

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between investigational product and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as the data become available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form
• Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate study intervention:

- Refrain from donating sperm.

  PLUS either:

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

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

- Is not a WOCBP (see definitions below in Section 10.4.3).

  OR

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

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

10.4.3. Woman of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

   - Documented hysterectomy;
   - Documented bilateral salpingectomy;
   - Documented bilateral oophorectomy.

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

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

2. Postmenopausal female:

   - A postmenopausal state is defined as age 60 years or older or no menses for 12 months without an alternative medical cause.
     - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT).
     - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device (IUD).
3. Intrauterine hormone-releasing system (IUS).
4. Bilateral tubal occlusion.
5. Vasectomized partner:
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.
6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - oral;
    - intravaginal;
    - transdermal;
    - injectable.
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral;
    - Injectable.
8. Sexual abstinence:
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for deoxyribonucleic acid (DNA) analysis.

The results of genetic analyses may be reported in the Clinical Study Report (CSR) or in a separate study summary, or may be used for internal decision making without being included in a study report.

The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained as indicated:

- Samples for specified genetic analysis (see Section 8.7.1) will not be stored beyond the completion of this study (eg, CSR finalization)].

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

Potential Cases of Drug-Induced Liver Injury

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

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

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

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

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

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

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

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

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

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum sample for acetaminophen drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the liver function test (LFT) abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

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

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That May Qualify as Adverse Events (AEs)
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 msec. • New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) Atrioventricular (AV) block of >30 seconds' duration. • Frequent premature ventricular complexes (PVCs), triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That May Qualify as Serious Adverse Events (SAEs)

• QTcF prolongation >500 msec.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset left bundle branch block (QRS >120 msec).
• New-onset right bundle branch block (QRS >120 msec).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free patients in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  • In awake, symptom-free patients with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer;
  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).

- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (rate <40 bpm), accelerated idioventricular rhythm (40< x <100), and monomorphic/polymorphic ventricular tachycardia >100 bpm (such as torsades de pointes).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as Serious Adverse Events

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

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

10.8. Appenidx 8: 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

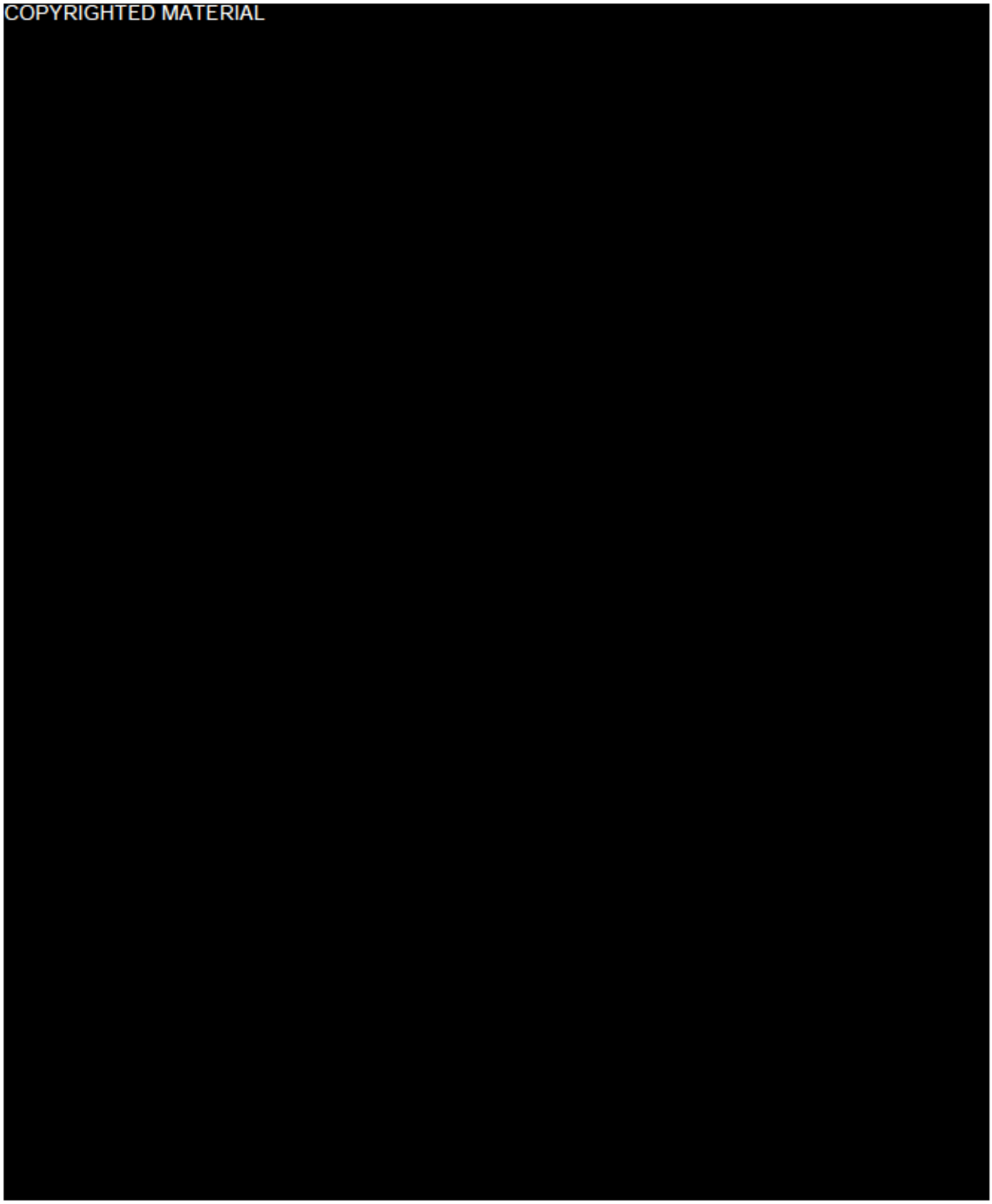
Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.

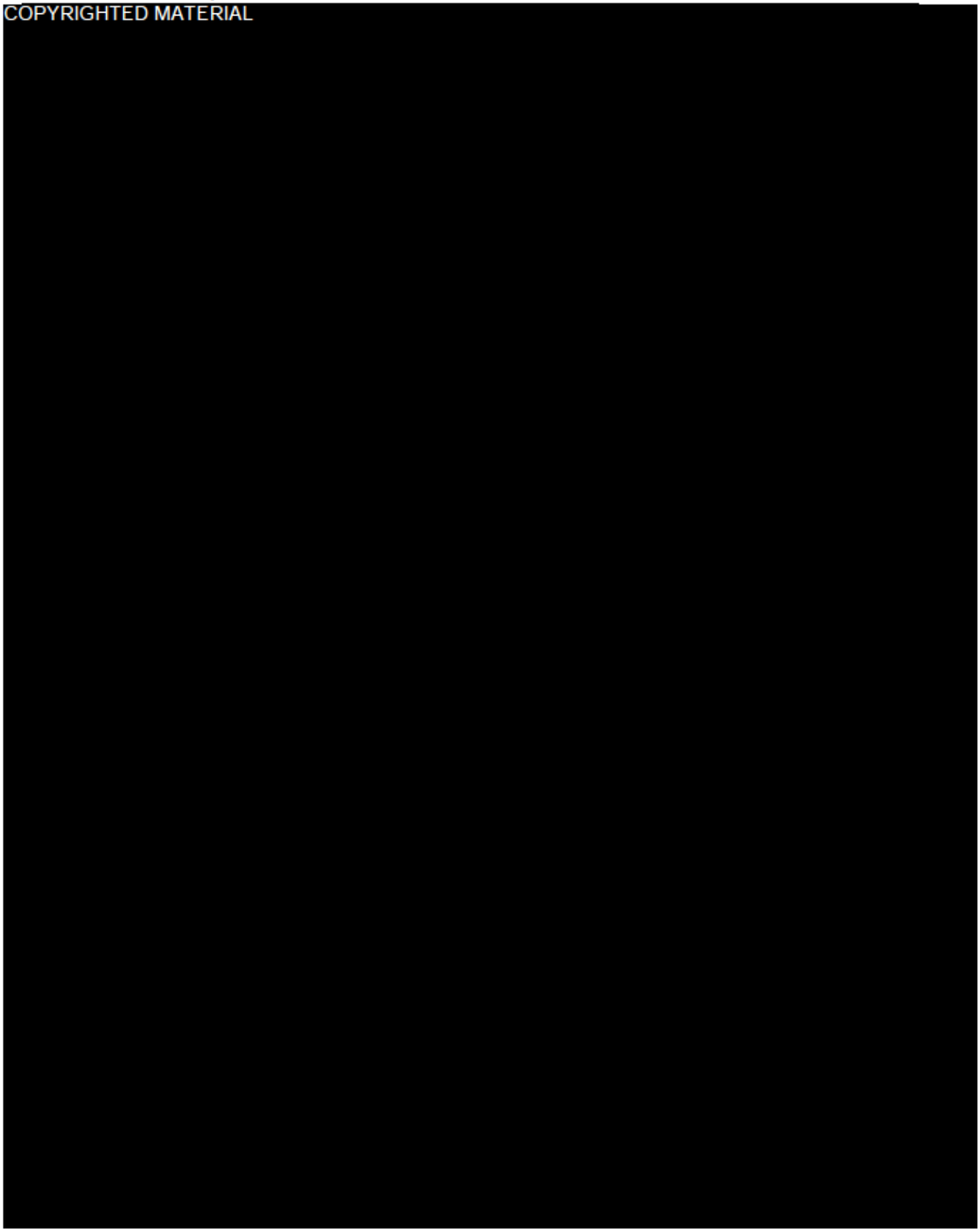
Class IV

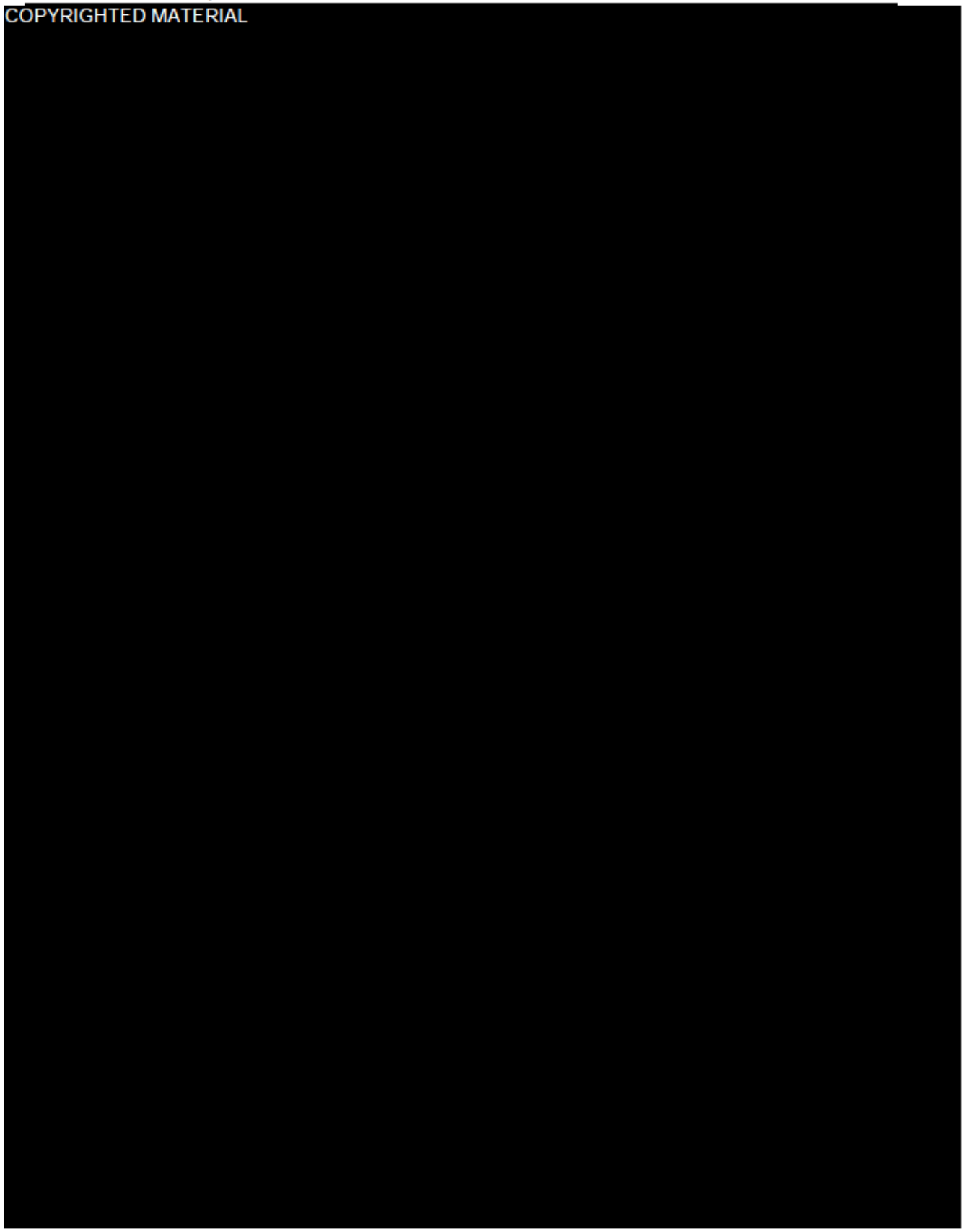
Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

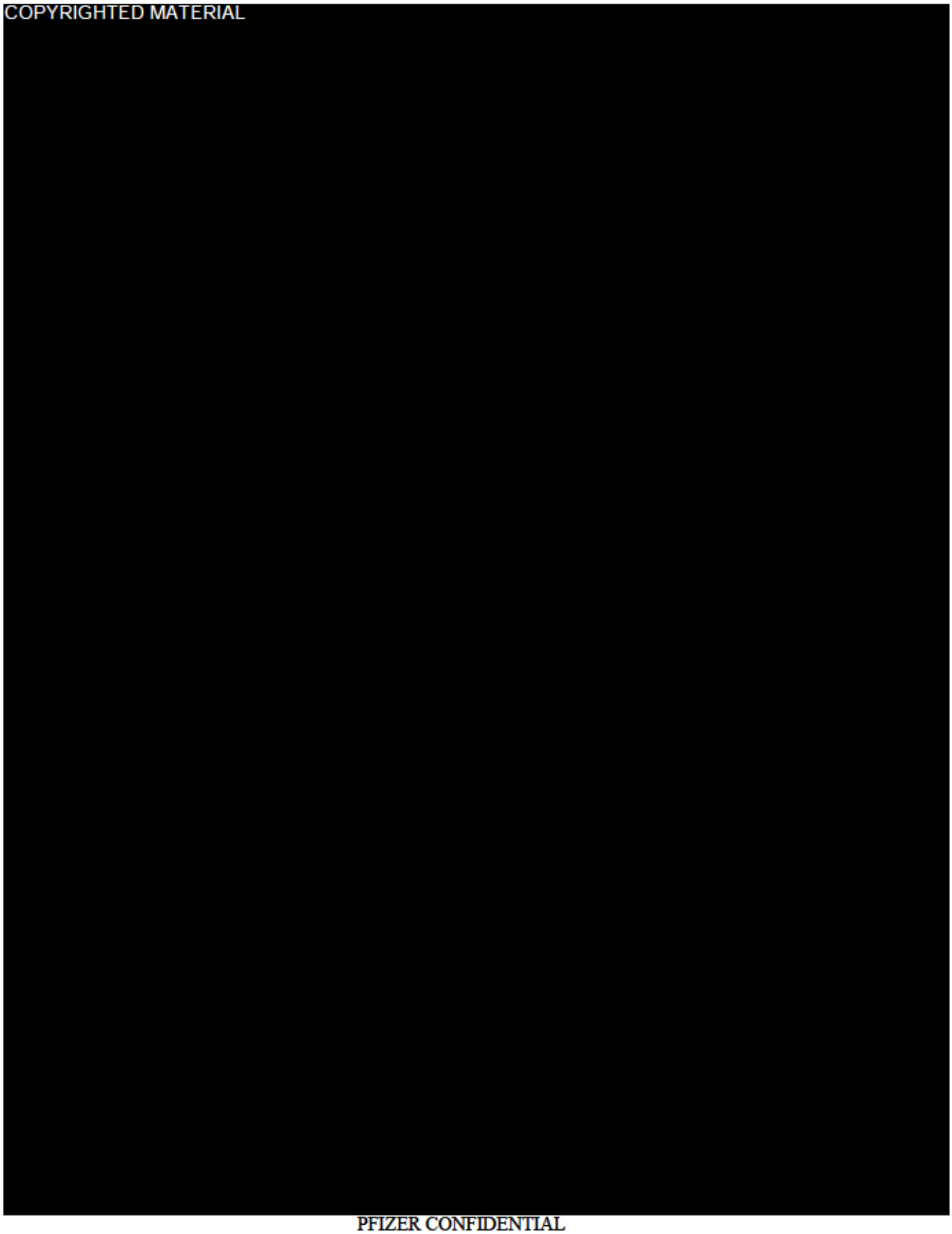
10.9. Appendix 9: Health Economics

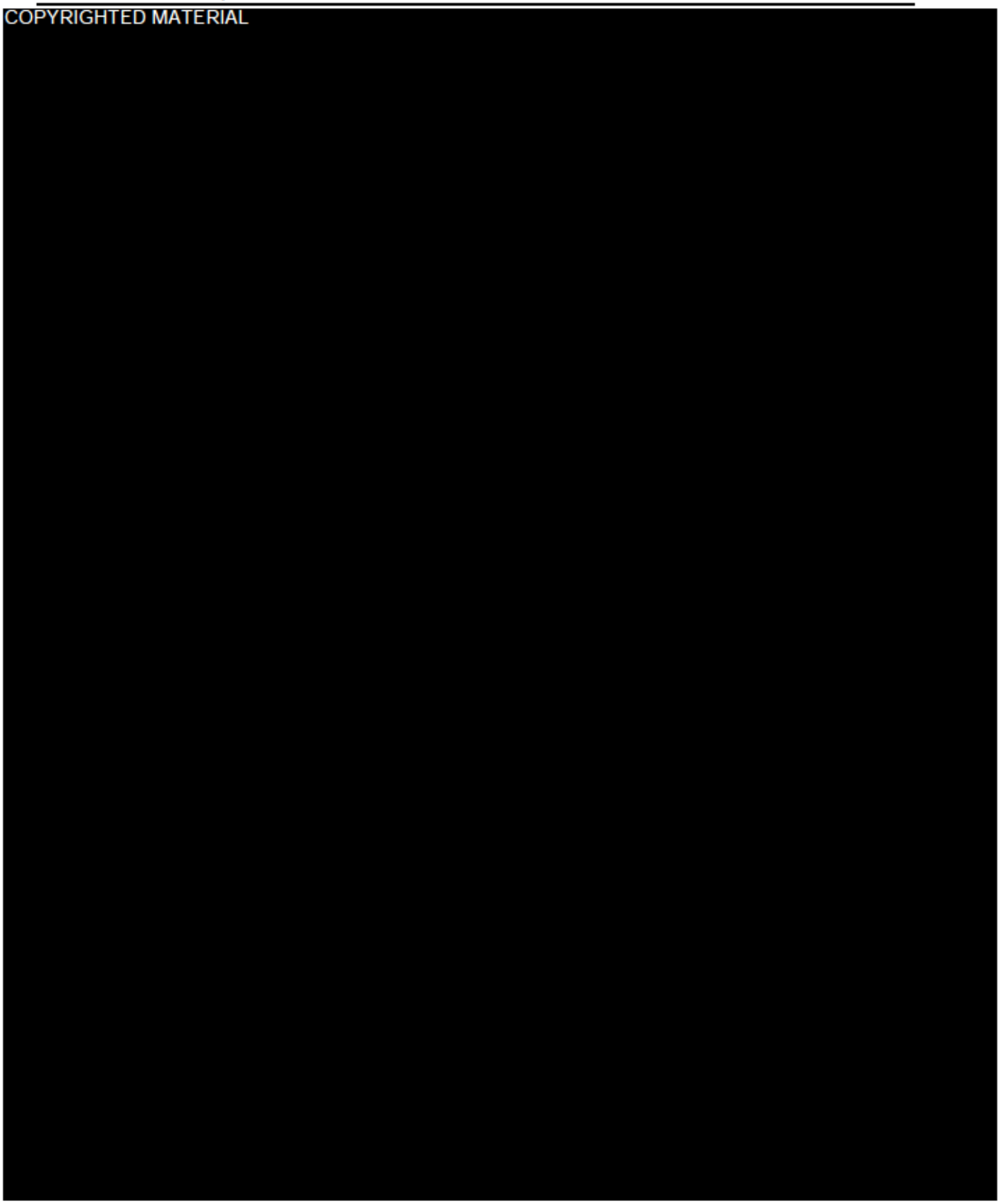
10.9.1. The Kansas City Cardiomyopathy Questionnaire Overall Score



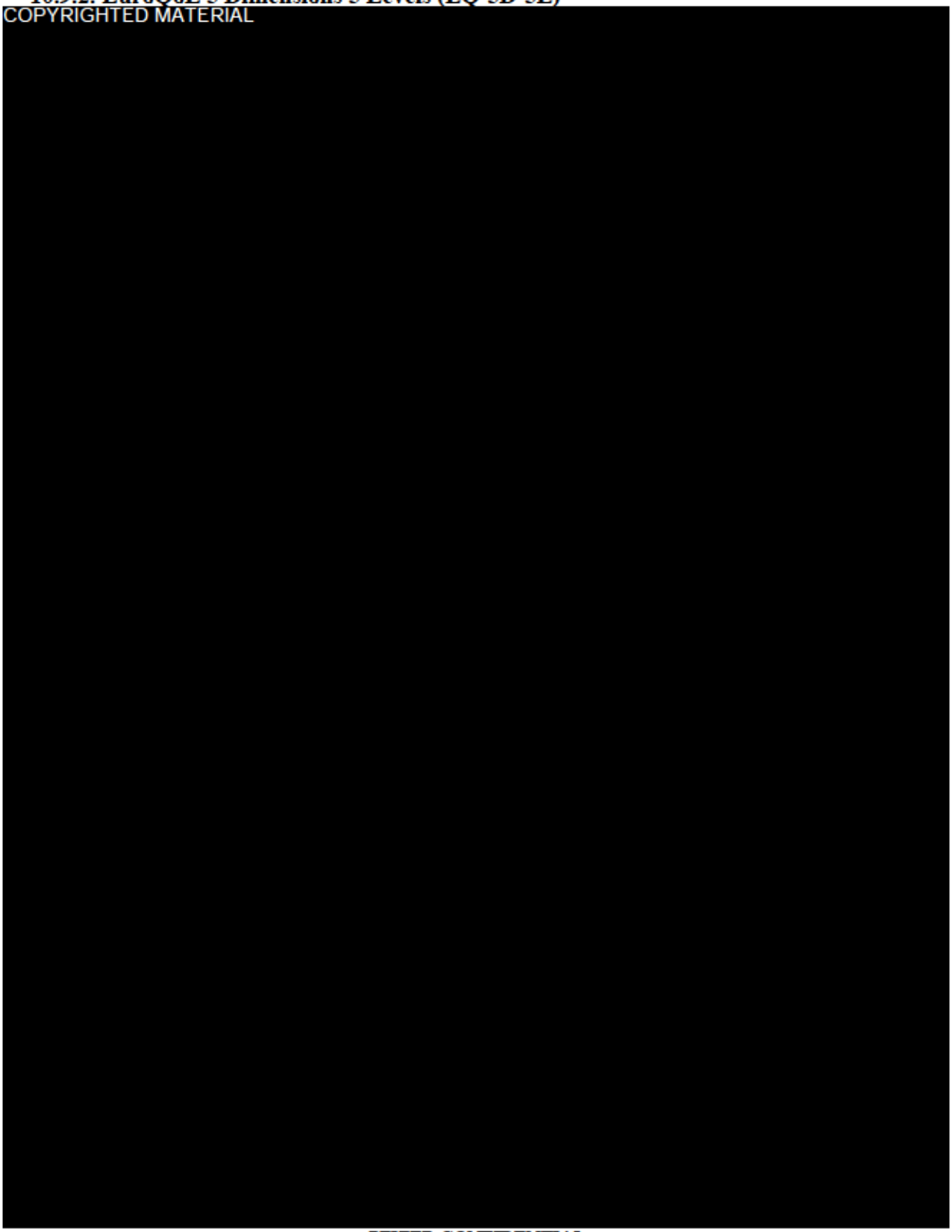


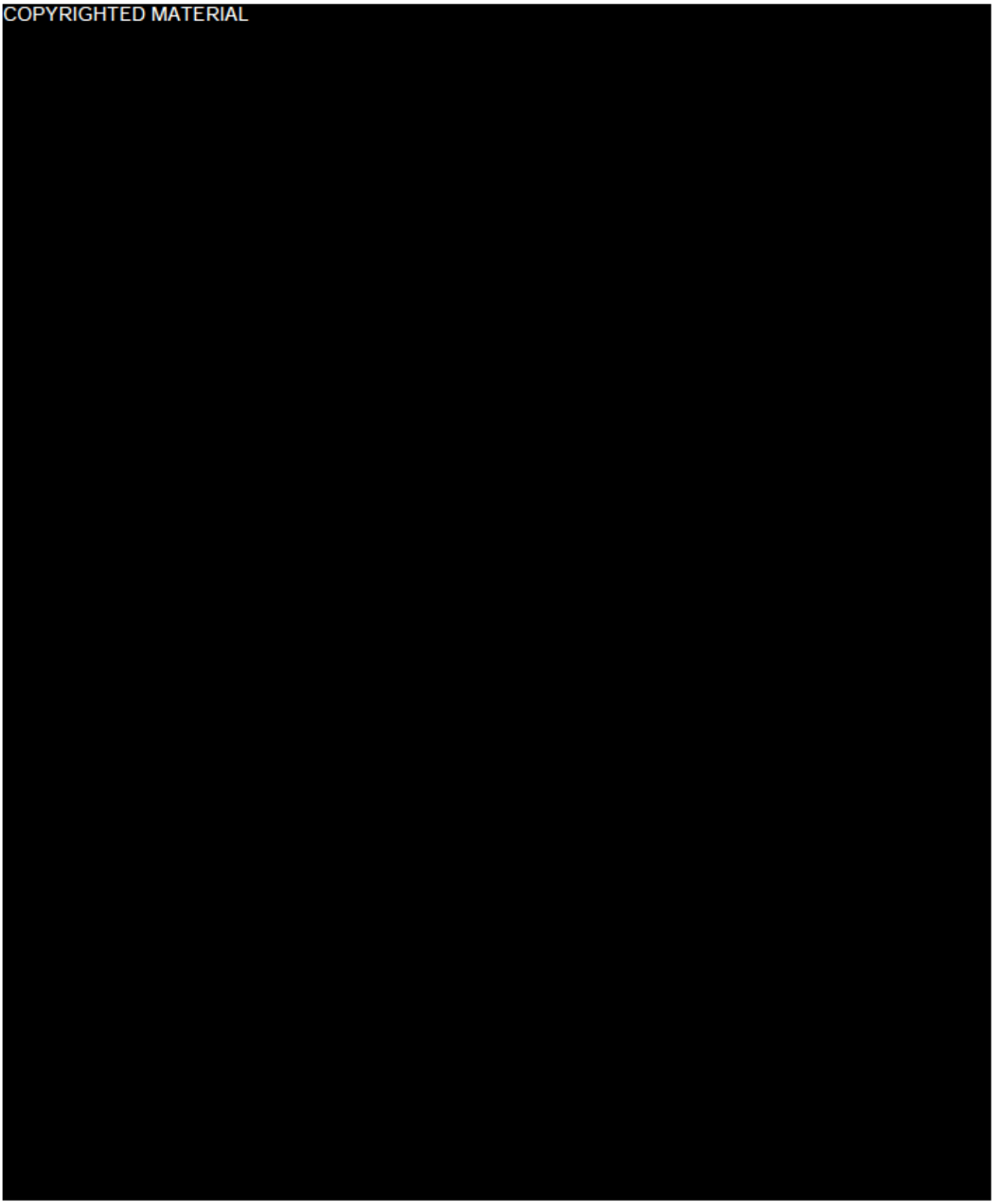


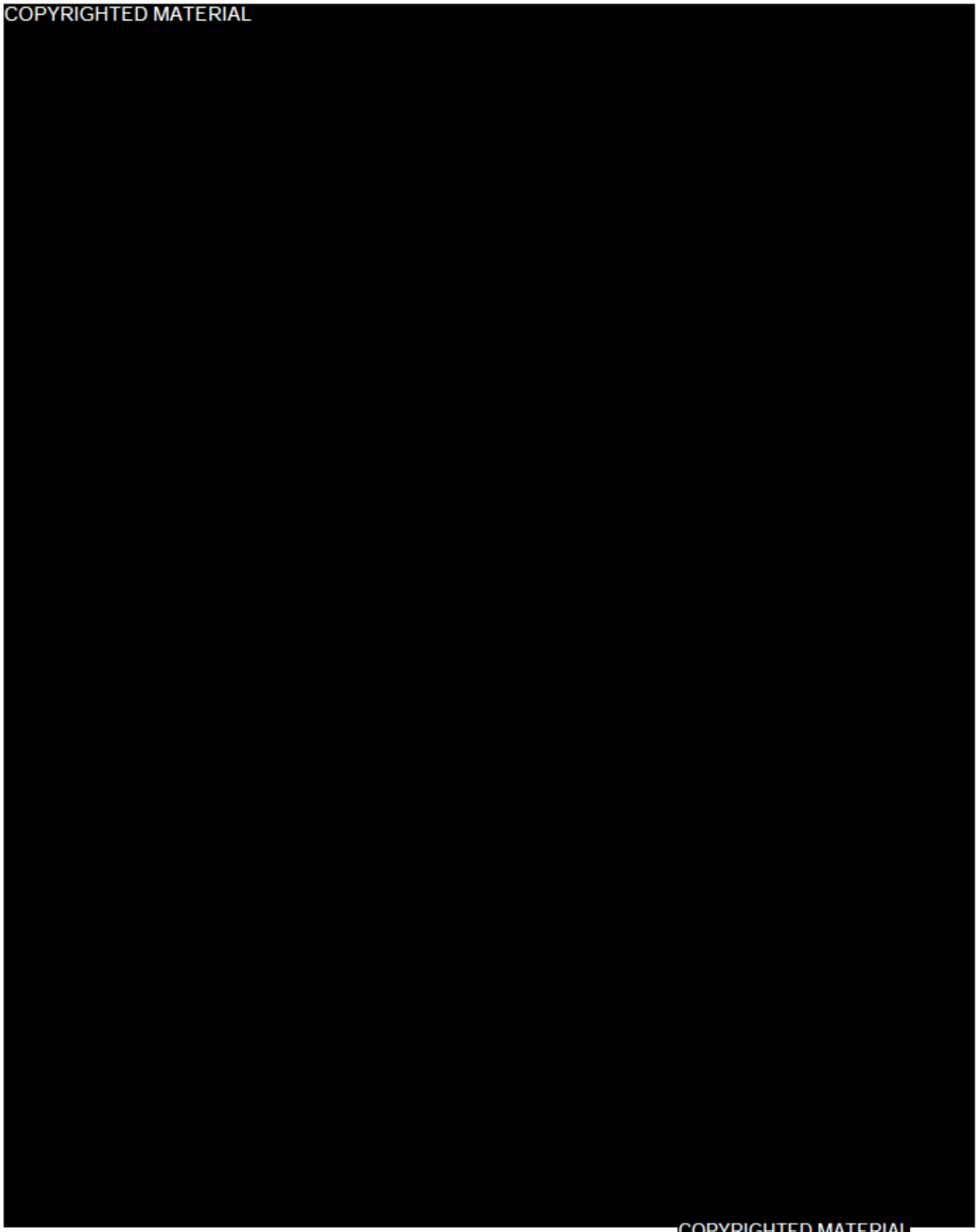




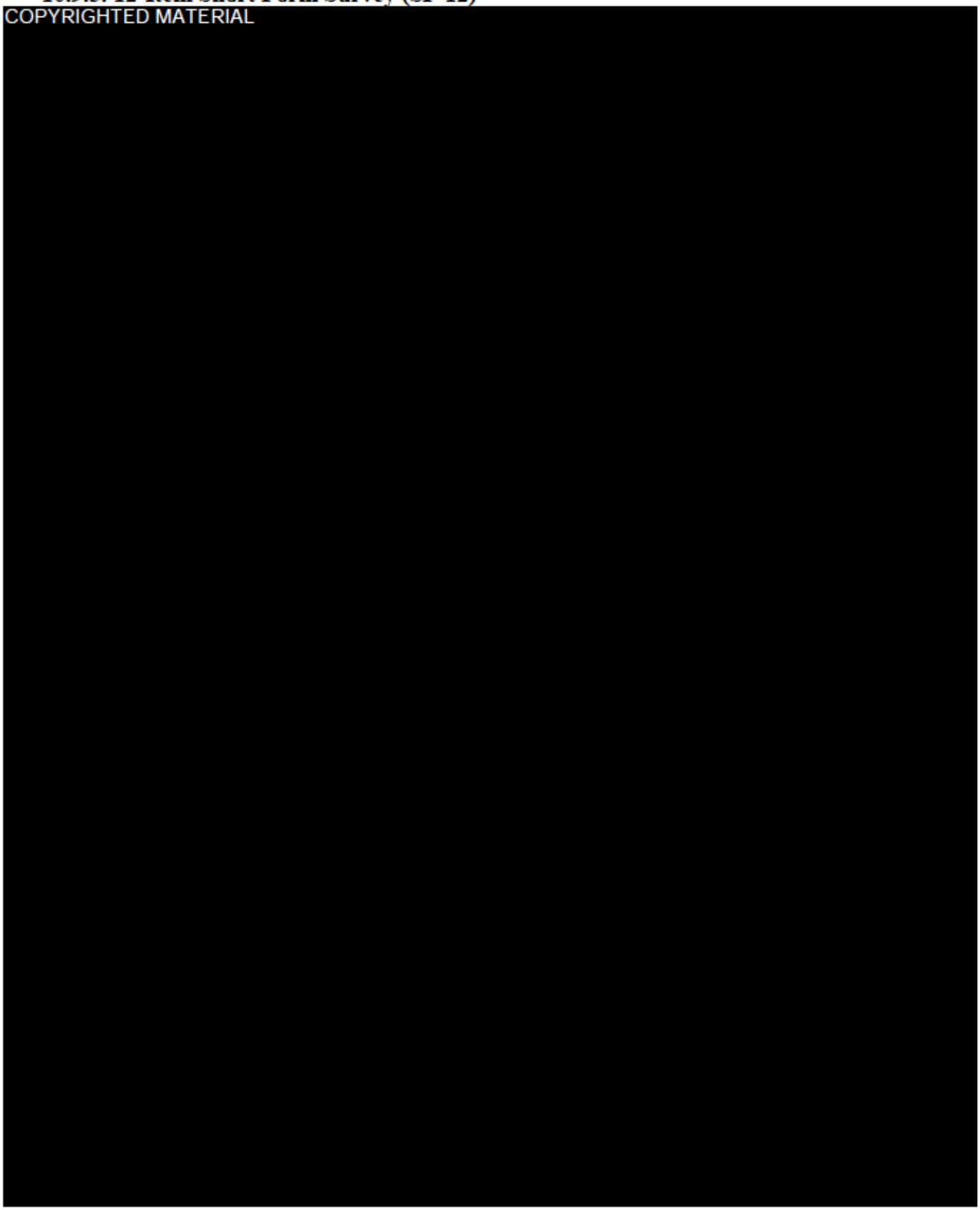
10.9.2. EuroQoL 5 Dimensions 5 Levels (EQ-5D-5L)

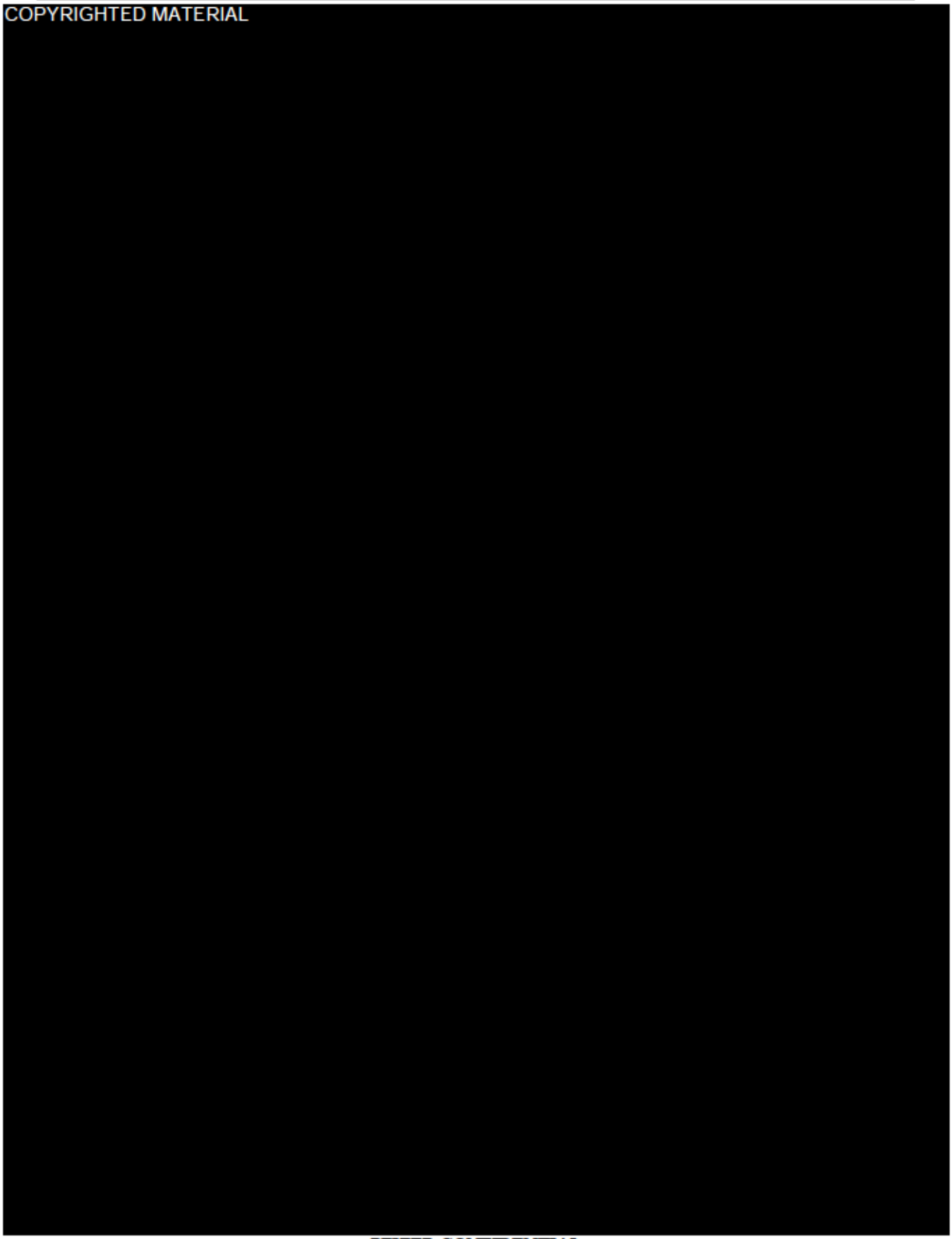


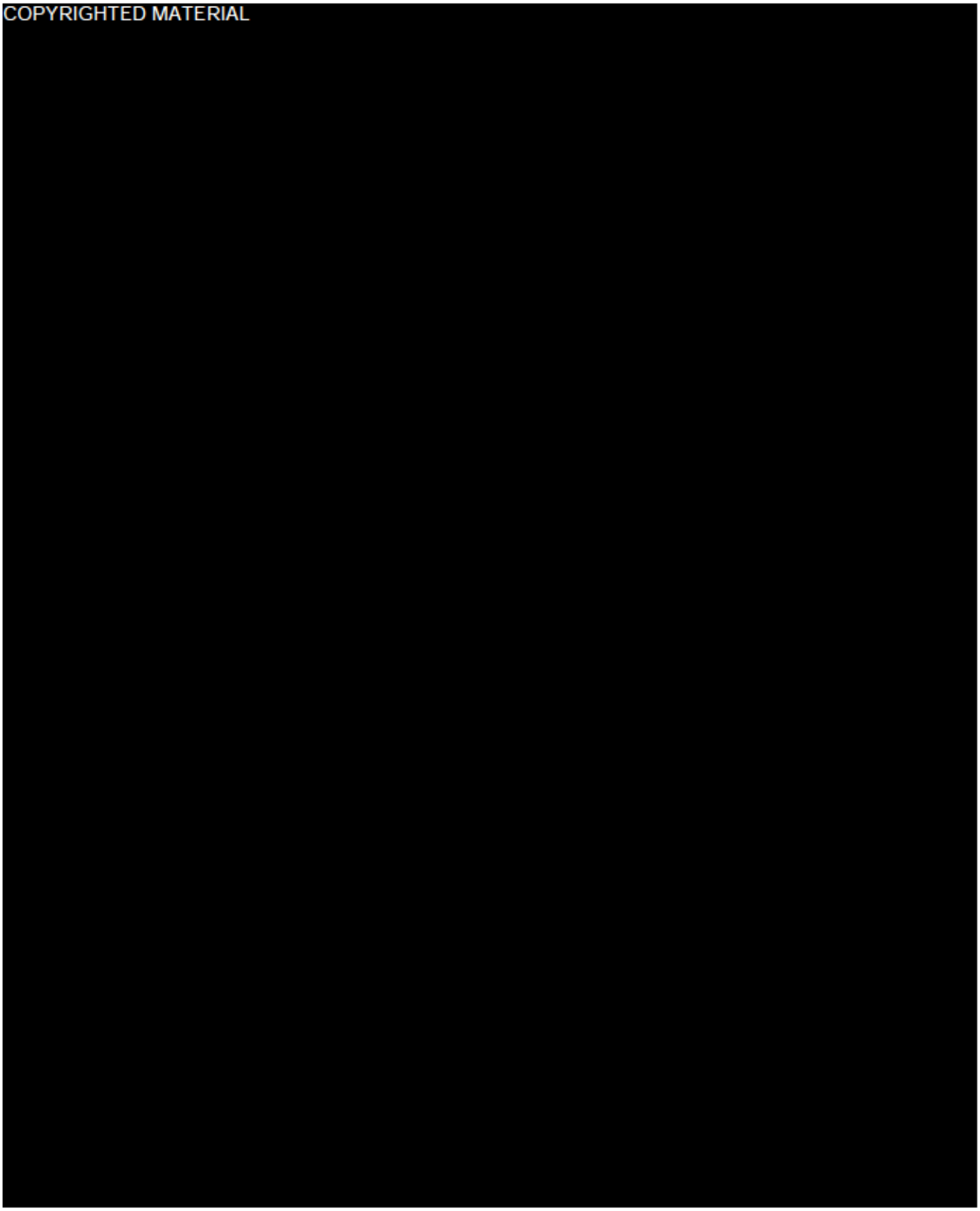




10.9.3. 12-Item Short Form Survey (SF-12)







10.10. Appendix 10: Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic globally and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

Investigators should continue to follow the protocol and data entry timelines. Any deviations to the protocol due to public emergencies, including the COVID-19， should be documented and recorded as deviations as requested by Health Authorities. When the situation permits, eg, quarantines or travel bans/advisories ceased, it is expected that participants go will return to their original study sites to complete an in-clinic visit indicated in Schedule of Activities (SoA) for the nearest missing visit (especially the visit of Month 12 or End of Treatment), even if the date is out of the scheduled visit window and some of the study measures have already been performed at an alternative facility.

10.10.1. Eligibility

While SARS-CoV2 testing is not mandated for this study, local clinical practice standards for testing should be followed. A patient should be excluded if he/she has a positive test result for SARS-CoV2 infection, is known to have asymptomatic infection, or is suspected of having SARS-CoV2. Patients with active infections are excluded from study participation as per **Exclusion Criteria 1 (medical conditions).** When the infection resolves, the patient should not be considered for re-screening. Individuals who has signed the ICD for participation in this study and are out of the screening window due to assessment of the eligibility due to public emergencies, including COVID-19, can be rescreened. All the screening, rescreening and baseline procedures should be done at the study sites, according to SoA.

10.10.2. Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the Schedule of Activities or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.

- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Sections 10.4 and 10.10.3.1 of this appendix regarding pregnancy tests.

Study participants must be reminded to promptly notify site staff about any change in their health status.

10.10.3. Alternative Facilities for Safety Assessments

Safety assessment, including complete physical examination (PE)/abbreviated PE, vital signs, laboratory tests, imaging, and ECGs can be performed at a local alternative facility if the investigator considered it as necessary and the study participant is unable to visit the study site, where allowable by law or local guidance. The specific alternative facility for each participant should be recommended by the investigator who has already had an alignment with the sponsor in a case by case basis.

All the results of safety assessments performed at a local alternative facility should be well documented and provided to the site staff as indicated in Sections 10.10.3.1, 10.10.3.2 and 10.10.3.3 below.

10.10.3.1. Laboratory Testing

If a study participant is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital. The following safety laboratory evaluations may be performed at a local laboratory:

Table 2. Protocol-Required Safety Laboratory Assessments permitted at a local laboratory

Hematology	Chemistry	Dipstick Urinalysis	Other
White blood cell count Hemoglobin Red blood cell count Neutrophils Lymphocytes Hematocrit Mean corpuscular volume Monocytes Mean corpuscular hemoglobin Eosinophils Mean corpuscular hemoglobin concentration Basophils Platelets	Sodium Inorganic Phosphorus Aspartate aminotransferase (AST) Potassium Glucose Gamma glutamyl transferase Chloride Total bilirubin Cholesterol Total protein Uric acid Blood Urea Nitrogen Albumin Thyroid-stimulating hormone Creatinine	pH Blood (free Hb) Ketones Glucose Bilirubin Protein Nitrite Specific gravity Urobilinogen	NT-pro BNP TnI International normalized ratio (INR) Prothrombin time (PT) Activated partial thromboplastin time (APTT) Fibrinogen (FIB)

Table 2. Protocol-Required Safety Laboratory Assessments permitted at a local laboratory

Hematology	Chemistry	Dipstick Urinalysis	Other
	Globulin Total thyroxine (T4) Calcium Alanine aminotransferase (ALT) Free T4 Retinol binding protein Alkaline Phosphatase		

It is expected that all participants should have protocol-specified safety laboratory tests performed per protocol SoA.

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

If a participant requiring pregnancy testing cannot visit a local laboratory for pregnancy testing, a home urine pregnancy testing kit with a sensitivity of at least 25 mIU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records and relevant data recorded on the CRF. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

10.10.3.2. Imaging

If the participant is unable to visit the study site for Echocardiography, the participant may visit an alternative facility to have the Echocardiography performed. Qualified study site personnel must order, receive, and review results.

10.10.3.3. Electrocardiograms

If the participant is unable to visit the study site for ECGs, the participant may visit an alternative facility to have the ECGs performed. Qualified study site personnel must order, receive, and review results.

10.10.4. Study Intervention

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study intervention must be considered.

Tafamidis may be shipped by courier to study participants if permitted by local regulations and in accordance with storage and transportation requirements for the tafamidis. Pfizer does not permit the shipment of tafamidis by mail. The tracking record of shipments and the chain of custody of tafamidis must be kept in the participant's source documents/medical records.

The study drug should only be permitted to be shipped to the participants after the assessments by the investigators. And the dispensed investigational product bottle should be collected at the next onsite visit.

10.10.5. Home Health Visits

A home health care service will not be utilized in this study.

10.10.6. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an adverse event (AE) or serious adverse events (SAE) and appropriate medical intervention provided. Study treatment should continue unless the investigator/treating physician is concerned about the safety of the participant, in which case temporary or permanent discontinuation may be required.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

10.10.7. Efficacy Assessments

Efficacy assessment, including 6-MWT, NT-pro BNP, Tropnin I can be performed at a local alternative facility if the investigator considered it as necessary and the study participant is unable to visit the study site, where allowable by law or local guidance. The study investigator can give instructions to the health care provider at a local alternative facility to keep the consistency of the assessment. The results of these assessments performed at a local alternative facility should be well documented and provided to the site investigators.

For patient report outcomes, including Kansas City Cardiomyopathy Questionnaire overall summary scores, EQ-5D-5L index scores and EQ-5D VAS scores, 12-Item Short Form Survey (SF-12) scores, paper scales will be mailed to the participant at the corresponding visit window, if the study participant is unable to visit the study site. The results will be reported by the participant in the scheduled visit window and mailed back to the investigator in a timely manner.

For TTR stabilization and TTR concentration assay, plasma concentrations of tafamidis, blood sample will not be collected at the alternative facility due to the complexity of sample management.

10.10.8. Independent Oversight Committees

This study will not use an Independent Oversight Committee.

10.11. Appendix 11: Abbreviations

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

Abbreviation	Term
6-MWT	6-minutes walk test
^{99m}Tc-PYP	99mTcpyrophosphate
AE	Adverse event
AL	Light chain amyloidosis
ALT	Alanine aminotransferase
Anti-HCV	hepatitis C antibody
Anti-HIV	Human immunodeficiency virus antibody
Anti-TP	Syphilis antibody
AST	Aspartate aminotransferase
ATTR-CM	Transthyretin amyloid cardiomyopathy
ATTR-PN	Transthyretin Amyloid Polyneuropathy
AUC	Area under the curve
AUC_{inf}	Area under the concentration-time curve from time 0 to infinity
AUC_{tau}	Area under the concentration-time curve over the dosing interval tau
AV	Atrioventricular
BA	Bioavailability
BBS	Biospecimen Banking System
BE	Bioequivalence
BMI	Body Mass Index
BP	Body pain
bpm	Beats per minute
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine kinase
C_{max}	Maximum observed drug concentration
$C_{max,ss}$	Maximum drug concentration at steady state
$C_{min,ss}$	Minimum drug concentration at steady state
CMC	Chemistry, Manufacturing, and Controls
CO_2	Carbon dioxide (bicarbonate)
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
CRO	Contract Research Organization
CRU	Clinical research unit
CSR	Clinical Study Report
CT	Clinical trial
cTNT	Cardiac troponin T

Abbreviation	Term
cTNI	Cardiac troponin I
CV	Cardiovascular
DCT	Data collection tool
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
DRE	Disease-related event
DU	Dispensable unit
E/A	Ratio of peak velocity blood flow from gravity in early diastole (the E wave) to peak velocity flow in late diastole caused by atrial contraction (the A wave).
EC	Ethics committee
ECG	Electrocardiogram
eCRF	electronic case report form
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EDR	extemporaneous dispensing record
EMA	European Medicines Agency
EOT	End of Treatment
EQ-5D VAS	EuroQoL 5 Dimensions visual analogue scale
EQ-5D-5L	EuroQoL 5 Dimensions 5 Levels
EU	European Union
EudraCT	European Clinical Trials Database
FOI	Fraction of initial tetramer concentration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GH	General health
HBsAg	Hepatitis B surface antigen
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HRT	Hormone replacement therapy
IB	Investigator's brochure
ICD	Informed consent document
ICH	International Council for Harmonisation
ID	Identification
IMP	Investigational medicinal product
IND	Investigational new drug
INR	International normalized ratio
IP manual	Investigational product manual
IRB	Institutional review board

Abbreviation	Term
IRC	Internal review committee
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IWR	Interactive Web-based response
K2EDTA	Dipotassium ethylenediaminetetraacetic acid
KCCQ	Kansas City Cardiomyopathy Questionnaire
LBBB	Left bundle branch block
LFT	Liver function test
LTE	Long-term extension
MATE	Multidrug and toxin extrusion transporter
mBMI	Modified Body Mass Index
MCS	Mental component summary score
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mental health
MHLW	Ministry of Health, Labor and Welfare
MR	Molar ratio
msec	Millisecond
N/A	Not applicable
NAb	Neutralizing antibodies
NIMP	Noninvestigational medicinal product
NSAID	Non-steroid anti-inflammatory drugs
NT-proBNP	N Terminal prohormone B type Natriuretic Peptide
NYHA	New Year Heart Association
OAT	Organic anion transporter
OATP	Organic anion-transporting polypeptide transporters
OCT	Organic cation transporter
PCD	Primary completion date
PCS	Physical component summary
PD	Pharmacodynamics(s)
PF	Physical function
PI	Principal Investigator
PK	Pharmacokinetic(s)
PR	PR interval
PT	Prothrombin time
PVC	Premature ventricular complex
QD	Once daily
QRS	QRS complex
QT	QT interval
QTc	Corrected QT
QTcF	Corrected QT (Fridericia method)
qual	Qualitative
RE	Role emotional

Abbreviation	Term
RNA	Ribonucleic acid
RP	Role physical
SAE	Serious adverse event
SAP	Statistical analysis plan
SF	Social function
SF-12	12-short item survey form
SoA	Schedule of activities
SOP	Standard operating procedure
SRSD	Single reference safety document
SUSAR	Suspected unexpected serious adverse reaction
TBili	Total bilirubin
TEAE	Treatment-emergent adverse events
TESPO	Tafamidis Enhanced Surveillance Pregnancy Outcomes
THAOS	Transthyretin-Associated Amyloidosis Outcomes Survey
TnI	Troponin I
TRACS	Transthyretin Amyloid Cardiac Study
TTR	Transthyretin
UGT	UDP glucuronosyltransferase
ULN	Upper limit of normal
US	United States
VT	Vitality
WOCBP	Women of childbearing potential

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