A SINGLE ARM, MULTICENTER, OPEN-LABEL STUDY TO EVALUATE THE EFFICACY, SAFETY, TOLERABILITY, AND PHARMACODYNAMICS OF ORALLY ADMINISTERED TAFAMIDIS MEGLUMINE IN TRANSTHYRETIN AMYLOID POLYNEUROPATHY PARTICIPANTS IN CHINA

Investigational Product Number:	PF-06291826
Investigational Product Name:	Tafamidis meglumine
United States (US) Investigational New Drug (IND) Number:	N/A
European Clinical Trials Database (EudraCT) Number:	N/A
Protocol Number:	B3461078
Phase:	4

Short Title: The Effect of Tafamidis Meglumine in Transthyretin Amyloid Polyneuropathy Participants

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
Amendment3	2 September 2021	The study intervention duration was **changed** from *48 weeks (Month 12* to *72 weeks Month 18)* CCI [redacted] The primaiy esbman en pomt was **changed** from "NIS-LL change from baseline at Week 48 (Month 12)" to "NIS-LL change from baseline at Week 72 (Month 18)". Secondaiy endpoints were **changed** from "NIS-LL at other visits than Week 48" to "NIS-LL at other visits than Week 72" and "Phaimacodynamics: TTR stabilization and TTR concentration at Day 1 (baseline), Week 8, Week 12, Week 24 and Week 48" to "Pha1macodynamics: TTR stabilization and TTR concenti·ation at Day 1 (baseline), Week 8, Week 12, Week 24, Week 48 and Week 72". The similar change was made in the following sections: • **Section 1.1 Synopsis** • **Section 1.3. Schedule of Activities (SoA)** • **Section 3 OBJECTIVES, ESTIMANDS, AND ENDPOINTS** • **Section 4 STUDY DESIGN** • **Section 8.6 Pharmacodynamics** • **Section 9.1.1.1 Primary Estimand** • **Section 10.9 Appendix 9: Alternative Measures During Public Emergencies** **Section 1.1 Synopsis:** • *Clinical visits will be scheduled at Baseline (Da 1 and at Week 4, Week 8,*

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
		Week 12, Week 24 and Week 48. was **changed** to *Clinical visits will be scheduled at Baseline (Day 1) and at Week 4, Week 8, Week 12, Week 24, Week 48, Week 60 and Week 72.* due to the extension of study duration. • *At Week 36 site visit, assessment of adverse events,* was **changed** to *At Week 36 and Week 60 site visit, assessment of adverse events,* due to the extension of study duration. • *between Week 48 and 60, and between Week 60 and 72* was **added** at the end of the last sentence in **Overall Design** in this section, due to the extension of study duration. • *During the treatment period, each partidpant will receive 20 mg tafamidis meglumine once daily for 48 weeks* was **changed** to *During the treatment period, each participant will receive 20 mg tafamidis meglumine once dai y for 72 weeks* due to the extension of study duration. **Section 1.3 Schedule of Activities (SoA):** • Two columns of *Week 60* and *Week 72 (or Early Study Discontinuation)* were **added** to the SoA to meet CDE's recommendation of "*Recommend* [redacted] and related assessments were also added to evaluate the efficacy, safety, tolerability and pha1macodynamics of tafamidis meglumine.

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
		• A new column of *End of Treatment* was **added**, because this visit is clinical important and the data is clinically valuable if participants withdraw the investigational treatment earlier. • *(or Early Study Discontinuation)* was **deleted** from column *Week 48*, because Early Study Discontinuation visit should be the same as Week 72. • *Echocardiography* was **added** in *Screening*, and Echocardiography at Baseline was **added** with a note *d*. Because Echocardiography 30 days prior to the baseline will be more feasible for the sites. • *d. All laboratory tests do not need to be repeated if acceptable screening assessment is performed within 30 days prior Day 1* was **changed** to *d. All the tests do not need to be repeated if acceptable screening assessment is performed within 30 days prior Day 1.* Because echocardiography is not a laboratory test. • *Between Week 12 to Week 24, Week 24 and 36, and between Week 36 and 48* was **changed** to *Between Week 12 to Week 24, Week 24 to Week 36, Week 36 to Week 48, Week 48 to Week 60, and between Week 60 to Week 72* in note 'i' due to the study duration extension. **Section 2.2.4 Clinical Overview:** the development program for Tafamidis was updated

		per the latest Investigator Brochure of Tafamidis as of March 2021. **Section 4.1 Overall Design:** all the clinical visits in this section were **updated** according to the new SOA, because the clinical visits increased due to the extension of study duration. **Section 5.2 Exclusion Criteria:** *eg,* was **added** before V*al122Ile, Leu111Met, Ile68Leu* in item 11, because there may be other cardiomyopathy specific TTR mutations newly detected. **Section 8. Study Assessments And Procedures: changed** amount of total blood sampling from approximately *150-200* ml to *200-250* ml, *provided the total volume taken during the study does not exceed 250 ml* was **changed** to *provided the total volume taken during the study does not exceed 300 ml,* due to study visit increase. **Section 8.1 Neuropathy Impairment Score-Lower Limb (NIS-LL):** the item numbers were **deleted** for NIS scale, and the item numbers were **updated** for NIS-LL, because NIS-LL instead of the full NIS scale is now appended in the protocol. The same change was also made in section **9.4.1.1 Neuropathy Impairment Score-Lower Limb (NIS-LL).** **Section 8.2.6.4 Echocardiograms:** *The assessment of end-diastolic interventricular septal thickness for study entry will be based on the echocardiogram performed at the Baseline visit. If the Baseline echocardiographic recording is not clear enough to accurately determine the end-diastolic interventricular septal wall thickness, it must be repeated*. was **deleted** from this section,

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
		because an Echocardiograms is not relevant to the study entry. **Section 10.2 Appendix 2: Clinical Laboratory Tests:** *Serum pregnancy testing* was **moved** from column *Chemistry* to column *Other* in *Table 1. Protocol-Required Safety Laboratory Assessments* per protocol template. **Section 10.9.3.1 Laboratory Testing:** *Serum pregnancy testing* was **moved** from column *Chemistry* to column *Other* in *Table 2. Protocol Required Safety Laboratory Assessments Permitted at a Local Laboratory* per protocol template.
Original protocol	01 June 2019	N/A

Please refer to Protocol Amendment History in Section 10.10 Appendix 10.

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: The Effect of Tafamidis Meglumine in Transthyretin Amyloid Polyneuropathy Participants

Rationale

Transthyretin amyloidosis is a protein misfolding disease with a broad spectrum of manifestations. When the peripheral nerves are affected predominately, the disease is termed transthyretin amyloid polyneuropathy (ATTR-PN). When the heart is primarily affected, the disease is called transthyretin amyloid cardiomyopathy (ATTR-CM). ATTR-PN is a fatal illness resulting from autosomal dominantly inherited single-point mutations on the transthyretin gene.

Tafamidis is a specific stabilizer of both variant and wild-type TTR. Tafamidis binds to TTR at the thyroxine binding sites and inhibits TTR tetramer dissociation, the rate limiting step in the amyloidogenic process. The result disrupts the amyloid cascade and fibril formation and interrupts disease progression.

In China, ATTR-PN is rare, estimated to affect approximately 1997 persons (with range from 435 to 10,134). In recent years, about 30-40 case reports have been published and several families impacted by ATTR-PN, with different TTR gene mutations from those observed in Europe were reported. Delay in the time to diagnosis is a major obstacle to the optimal management of ATTR-PN in China, where typically patients are correctly diagnosed several years after the emergence of first clinical sign of the disease. Given the significant unmet medical need, it is critical to raise disease awareness, to facilitate earlier diagnosis and urgently enable access to treatment of this potentially fatal disease.

Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
Primary:		
To evaluate the effect of tafamidis meglumine on clinical efficacy in ATTR-PN participants.	Descriptive statistics of the NIS-LL change from baseline at Week 72 (Month 18), regardless of whether or not participant continues with/adheres to treatment	Change from baseline NIS-LL at Week 72 (Month 18)

Objectives	Estimands	Endpoints
Secondary:		
To evaluate the efficacy, safety, tolerability, and pharmacodynamics of tafamidis meglumine in ATTR-PN participants.	Descriptive statistics of the secondary endpoints in ATTR-PN participants, regardless of whether or not participant continues with/adheres to treatment.	Efficacy: Change from baseline at follow-up visit on the following scales: • NIS-LL at other visits than Week 72 • TQOL score and 5 domains as measured by the Norfolk QOL – Diabetic Neuropathy (Norfolk QOL-DN); • Modified Body Mass Index (mBMI); • 36-item short form (SF-36); • EQ-5D-5L Index Score. Safety: Adverse events, vital signs (temperature, blood pressure, pulse rate, and respiratory rate), ECGs, ECHO, clinical laboratory evaluations. Pharmacodynamics: TTR stabilization and TTR concentration at Day 1 (baseline), Week 8, Week 12, Week 24, Week 48 and Week 72.

Overall Design

This is a single-arm, open-label, multicenter study designed to evaluate the efficacy, safety, tolerability as well as pharmacodynamics of tafamidis meglumine in ATTR-PN participants in China.

All enrolled participants will receive oral tafamidis meglumine 20 mg soft capsules once daily starting on Day 1. Clinical visits will be scheduled at Baseline (Day 1) and at Week 4, Week 8, Week 12, Week 24, Week 48, Week 60 and Week 72. At Week 36 and Week 60 site visit, assessment of adverse events, safety related lab testings, concomitant medications and investigational product compliance will be scheduled. Every 6 weeks (do not exceed 7 weeks since last confirmation) telephone contacts will be made during visits in which no

investigative site visits are scheduled for assessment of adverse events, concomitant medications and investigational product compliance (between Week 12 and 24, between Week 24 and 36, between Week 36 and 48, between Week 48 and 60, and between Week 60 and 72).

Number of Participants

Approximately 10--15 participants are planned to be enrolled and all of them will be assigned to investigational product. CCI [redacted]

Intervention Groups and Duration

The study starts with the signing of the infonned consent document, and is divided into 3 periods, including: screening period (Day-30 to Day 0), treatment period (72 weeks), and follow-up period (28 days after last dose).

During the treatment period, each participant will receive 20 mg tafamidis meglumine once daily for 72 weeks.

Data Monitoring Committee: No

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

Statistical Methods

Descriptive statistics summaiy will be done for all the study endpoints. The analysis will be done at the end of the study with no interim analysis planned.

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.

Activity	Screening	Day 1 Baseline	Week 4 (Day 28)	Week 8 (Day 56)	Week 12 (Day 84)	Week 24 (Day 168)	Week 36 (Day 252)	Week 48 (Month 12/Day 336)	Week 60 (Month 15/Day 420)	End of treatment	Week 72 (Month 18/Day 504) (or Early Study Discontinuation)	Post-study follow-up (28 days after last dose)
Allowable window	Day -30-0		±7 days	±7 days	±7 days	±14 days	±14 days	±14 days	±14 days	+14 days	±14 days	+7 days
Informed consent	X											
Medical history/ demographics	X											
Review of entrance criteria	X	X										
Registration	X	X										
Biopsy to confirm amyloid	X[a]											
Confirmation of Val30Met or non-Val30	X											

Activity	Screening	Day 1 Baseline	Week 4 (Day 28)	Week 8 (Day 56)	Week 12 (Day 84)	Week 24 (Day 168)	Week 36 (Day 252)	Week 48 (Month 12/Day 336)	Week 60 (Month 15/Day 420)	End of treatment	Week 72 (Month 18/Day 504) (or Early Study Discontinuation)	Post-study follow-up (28 days after last dose)
Allowable window	Day -30-0		±7 days	±7 days	±7 days	±14 days	±14 days	±14 days	±14 days	+14 days	±14 days	+7 days
Met genotype												
Serology (HBsAg, HIV antibodies, HCV antibodies)	X											
Complete physical examination (PE)	X					X		X			X	
Abbreviated PE		X	X	X	X		X		X	X		
Body height	X											
Body weight	X	X	X	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	
Blood sample for TTR stabilization assay, TTR concentration		X[b]		X[c]	X[c]	X[c]		X[c]		X[c]	X[c]	

Activity	Screening	Day 1 Baseline	Week 4 (Day 28)	Week 8 (Day 56)	Week 12 (Day 84)	Week 24 (Day 168)	Week 36 (Day 252)	Week 48 (Month 12/Day 336)	Week 60 (Month 15/Day 420)	End of treatment	Week 72 (Month 18/Day 504) (or Early Study Discontinuation)	Post-study follow-up (28 days after last dose)
Allowable window	Day -30-0		±7 days	±7 days	±7 days	±14 days	±14 days	±14 days	±14 days	+14 days	±14 days	+7 days
Laboratory tests (hematology, serum chemistry, TSH, total T4, free T4, RBP, and urinalysis)	X	X[d]	X	X	X	X	X	X		X	X	
NT-pro-BNP, Troponin I/T, coagulation panel	X	X[d]		X		X		X		X	X	
Contraception check: serum pregnancy test (females of child-bearing potential only)	X		X	X	X	X	X	X		X	X	

Activity	Screening	Day 1 Baseline	Week 4 (Day 28)	Week 8 (Day 56)	Week 12 (Day 84)	Week 24 (Day 168)	Week 36 (Day 252)	Week 48 (Month 12/Day 336)	Week 60 (Month 15/Day 420)	End of treatment	Week 72 (Month 18/Day 504) (or Early Study Discontinuation)	Post-study follow-up (28 days after last dose)
Allowable window	Day -30-0		±7 days	±7 days	±7 days	±14 days	±14 days	±14 days	±14 days	+14 days	±14 days	+7 days
Contraception check: urine pregnancy test (females of child-bearing potential only)		X							X			
Serum FSH[e]	X											
12-Lead ECG	X	X		X		X	X	X		X	X	
Echocardiography	X	X[d]				X		X			X	
Karnofsky Performance Status Scale	X											
NIS-LL[f]		X[g]				X		X		X	X	
EQ-5D-5L		X				X		X			X	
SF-36		X				X		X			X	
Norfolk QOL-DN		X				X		X			X	
Dispense investigational product		X[h]	X	X	X	X	X		X			
Collect all dispensed investigatio			X	X	X	X	X	X	X	X	X	

Activity	Screening	Day 1 Baseline	Week 4 (Day 28)	Week 8 (Day 56)	Week 12 (Day 84)	Week 24 (Day 168)	Week 36 (Day 252)	Week 48 (Month 12/Day 336)	Week 60 (Month 15/Day 420)	End of treatment	Week 72 (Month 18/Day 504) (or Early Study Discontinuation)	Post-study follow-up (28 days after last dose)
Allowable window	Day -30-0		±7 days	±7 days	±7 days	±14 days	±14 days	±14 days	±14 days	+14 days	±14 days	+7 days
nal product bottle												
Concomitant treatment(s)[i]	X	X	X	X	X	X	X	X	X	X	X	
Study medication compliance[i]		X	X	X	X	X	X	X	X	X	X	
Serious and non-serious adverse events monitoring[i]	X	X	X	X	X	X	X	X	X	X	X	X[j]

Abbreviations: Val30Met=substitution of methionine for valine at position 30; PE: physical examination; HBsAg=hepatitis B surface antigen; HIV=human immunodeficiency virus; HCV=Hepatitis C virus; TTR: transthyretin; TSH = thyroid-stimulating hormone; T4 = thyroxine; RBP = Retinol-binding protein; NT-pro-BNP = N-terminal B-type natriuretic peptide; FSH=follicle stimulating hormone; ECG= electrocardiogram; NIS-LL=Neuropathy Impairment Score-Lower Limb; EQ-5D-5L: EuroQoL 5 Dimensions 5 Levels; Norfolk QOL-DN=Norfolk Quality of Life Diabetic Neuropathy; SF-36: 36-Item Survey

a. Biopsy must have been performed within 5 years of enrollment. If greater than 5 years, biopsy must be repeated at the investigative site.

b. Baseline (Day 1) sample: collect pre-dose during the clinic visit. The actual pre-dose blood sampling time and the time of first dose taken will be recorded.

c. Collect samples during site visit. Refer to the chronology of events in Section 8. At site visit, the time of last dose taken prior to blood collection for TTR stabilization assay and TTR concentration will be checked and recorded. The actual blood sampling time will be recorded.

d. All the tests do not need to be repeated if acceptable screening assessment is performed within 30 days prior Day 1.

e. Performing only on 45-60 year old females who have been amenorrhea for at least 2 years.

f. NIS-LL testing is performed 2 times at least 24 hours apart within a 1-week period by the same neurologist.

g. Baseline evaluations maybe performed during the screening period only in cases where scheduling did not permit the examinations at baseline.

h. All the assessments and procedures at Day 1 (baseline) visit in the SoA should be completed prior to the investigational product administration on Day 1. Only on Day 1, the investigational product will be administered at site during clinic visit.

i. Between Week 12 to Week 24, Week 24 to Week 36, Week 36 to Week 48, Week 48 to Week 60, and between Week 60 to Week 72, every 6 weeks telephone contact (with a window of ±7 days) to monitor for adverse events, study medication compliance and concurrent medications (refer to Section 8.3).

j. Telephone contact can be used to monitor for adverse events.

2. INTRODUCTION

Tafamidis binds with negative cooperativity to the 2 transthyretin (TTR) thyroxine binding sites and has been developed as an oral specific stabilizer of TTR tetramer that is cmTently used for the treatment of patients with stage 1 symptomatic polynemopathy to delay nemologic impaitment.

In August 2018, the Notice on Soliciting Opinions on List of New Drngs with Urgent Clinical Need Marketed Overseas announced that tafamidis for ATTR-PN was included in the NMPA (National Medical Products Administration) List of 48 products for which there was an mgent clinical need in China.

CCI [redacted] This study is designed to evaluate the efficacy, safety, tolerability as wel l as pharmacodynamics of tafamidis participants in China CCI [redacted]

2.1. Study Rationale

CCI [redacted] and is designed to evaluate the efficacy, safety, tolerability and pha1macodynamics of tafamidis meglmnine in ATTR-PN participantsin China. The treatment dose and regimen requit·ed in protocol are aligned with the approved label in China.

Complete info1mation for this compound may be found in the single reference safety document, which for this study is the Investigator Brochure (IB).

2.2. Background

2.2.1. Disease Introduction

Transthyretin amyloidosis is a protein misfolding disease with a broad spectrnm of manifestations. When the peripheral nerves are affected predominately, the disease is te1med transthyretin amyloid polynemopathy (ATTR-PN). ATTR-PN is a fatal illness resulting from autosomal dominantly inherited single-point mutations on the transthyretin gene.

The main feature of ATTR-PN, regardless of genetic mutation, ethnic background, or geographic location, is a progressive, length-dependent degenerative sensorimotor and autonomic neuropathy.[1-7] Symptoms of ATTR-PN often start as non-specific numbness or pain in the extremities, which progresses to include more severe senso1y distmbances, motor weakness and autonomic dysfunction. Time-to-diagnosis in non-endemic regions, such as the US (United States), has been estimated at 4 years.[8]

This constellation of sympto1111s has a devastating impact on adults stricken with ATTR-PN in the prime of then·lives. Paiiicipant typically die from progressive and relentless worsening of nemopathy, seconda1y infections, cachexia, or sudden death.[9,10]

This disease typically strikes people in their 30s to 50s. A person affected by this disease will develop a slow, steady, and devastating neurologic decline leading ultimately to death. Rates of disease progression can vary somewhat by mutation, with mean survival of 10 to 15 years following symptom onset for participants with Val30Met mutation and 3 to 13 years for participantswith non-Val30Met mutations.[10]

2.2.2. Treatment of ATTR-PN

Tafamidis is a specific stabilizer of both variant and wild-type TTR. Tafamidis binds to TTR (also referred to as pre-albumin) at the thyroxine binding sites and inhibits TTR tetramer dissociation, the rate limiting step in the amyloidogenic process. The result disrupts the amyloid cascade and fibril formation and interrupts disease progression. It has been developed as an oral specific stabilizer of TTR tetramer.

In 2011 tafamidis became the first pharmacotherapy available for ATTR-PN when it was approved in the EU (European Union) under Exceptional Circumstances and it was approved to treat ATTR-PN in Japan on 20 September 2013 and on 05 February 2020 in China. Tafamidis is also approved in the following countries: Argentina, Brazil, Colombia, Hong Kong, Israel, Macau, Macedonia, Mexico, Russia, Serbia and South Korea and it remains the only orally administered small molecule that has been approved to treat ATTR-PN.

2.2.3. ATTR-PN in China

In China, ATTR-PN is rare, estimated to effect approximately 1997 persons (with range from 435 to 10,134).[11] In the 1990s, the first ATTR-PN kindred was diagnosed in Peking Union Medical College Hospital.[12] In recent years, about 30-40 case reports have been published and several families impacted by ATTR-PN with different TTR gene mutations from those observed in Europe were reported.[13-17]

Several factors, including the rarity of the disease in the general population, a lack of awareness among physicians of variable clinical features, and limited access to diagnostic tools (ie, histopathological and genetic screening) contribute to high rates of misdiagnosis and poorer patient outcomes. Common initial misdiagnoses of ATTR-PN include idiopathic axonal polyneuropathy, chronic inflammatory demyelinating polyneuropathy, and lumbar spinal stenosis. Diabetes or chronic alcoholism may induce polyneuropathies similar to ATTR-PN. Further potential misdiagnoses include Charcot–Marie–Tooth neuropathy or motor neuron disease.

Delay in the time to diagnosis is a major obstacle to the optimal management of ATTR-PN in China, where typically patients are correctly diagnosed several years after the emergence of first clinical sign of the disease. Given the significant unmet medical need, it is critical to raise disease awareness, to facilitate earlier diagnosis and urgently enable access to treatment of this potentially fatal disease.

In August 2018, the Notice on Soliciting Opinions on List of New Drugs with Urgent Clinical Need Marketed Overseas announced that tafamidis for ATTR-PN was included in the NMPA List of 48 products for which there was an urgent clinical need in China.

2.2.4. Clinical Overview

As of March 2021, the development program for tafamidis includes 20 Phase 1 studies, in healthy paiticipants (19 studies) and hepatically impaired paiticipants (1 study), 1 controlled and 4 uncontrolled studies in paiticipants with ATTR-PN, 1 controlled and 3 uncontrolled studies in paiticipants with ATTRCM, and 6 noninterventional studies in ATTR paiticipants. Cumulatively, it is estimated that 2356 pa1ticipants have paiticipated in the tafamidis clinical development program: 2146 paiticipants were exposed to tafainidis.

Data demonstrating the efficacy oftafamidis for the treatment of ATTR-PN are derived from 1 pivotal Phase 3, randomized placebo-controlled, efficacy and safety study (Study Fx-005) in which a total of 65 paiticipants (with the Val30Met mutation) were randomized to tafainidis for 18 months, as well as data from the extension to Study Fx-005, ie, Study Fx-006, in which data from paiticipants originally treated with placebo and then switched to tafamidis treatment provide fmther evidence of efficacy in a more severely affected pa1ticipants population and the sustainability of the treatment effect in paiticipants who were on tafamidis for a full 30 months.

A suppo1tive Phase II study (uncontrolled Study FxlA-201) enrolled 21 ATTR-PN paiticipants (with mutations other than Val30Met) who were treated with tafamidis for up to 12 months. Each clinical study has been followed by a single treatment aim extension study designed to provide long-te1m data (safety and efficacy) of treatment with tafamidis meglumine 20 mg QD (Once daily) (Study FxlA-303). All efficacy studies were perfo1med using the -soft capsule fo1mulation at the dose of 20 mg daily; therefore, no in vitro - in vivo conelation studies were waiTanted.

2.3. Benefit/Risk Assessment

More detailed infonnation about the known and expected benefits and risks and reasonably expected adverse events (AEs) of tafainidis may be found in the investigator's brochure, which is the single reference safety document (SRSD) for this study.

2.3.1. Benefit

The benefits of treatment with tafamidis include:

- Tafamidis was well-tolerated and demonstrated an acceptable safety profile in healthy volunteer studies, the pivotal study of patients with ATTR-PN, and the suppo1tive patient studies conducted. There were few serious adverse events, with no change in the safety profile following longer te1m treatment.
- [redacted] Study Fx-005 [redacted] Progression rates for the pa1ticipants treated with tafamidis were statistically significantly less than those for placebo-treated paiticipants for key efficacy pai·ameters. The slower progression rate translated to preserved neurologic function in tafainidis paiticipants compai·ed with untreated participants.

- In the Efficacy Evaluable population in Study Fx-005, 60% percent of ATTR-PN participants administered tafamidis had no progression of neurological impairment(as demonstrated by the NIS-LL(Neuropathy Impairment Score - Lower Limb)), compared with 38% of participants on placebo. Similar rates of response were observed after 30 months of treatment (and therefore demonstrating durability of effect to the medication over time).

- Evidence of treatment effect was observed as early as Week 24 for certain outcomes (eg, neurophysiological tests), with persistence of effect across all outcome measures demonstrated through 30 months of treatment.

- The rate of deterioration of neurologic function was decreased by 52%, and that for neurophysiological function by 84% for small fiber and 54% for large fiber, and was maintained over 30 months of follow-up. These results are clinically relevant, and represent better neurologic status in those on tafamidis at the end of 18 months compared with placebo. Importantly, the observed decrease in rate of progression would be expected to translate to maintained functional status longer term.

- Improvement in nutritional status and long-term maintenance of mBMI(modified body mass index) and maintenance of effect through 30 months of follow-up. This is a critical effect, as low mBMI is clearly associated with worse outcomes in participants with ATTR-PN.

- In the most relevant population in Study Fx-005, participant reported quality of life was maintained, with persistence of effect over 30 months of follow-up in Study Fx-006.

- Earlier treatment with tafamidis resulted in better neurologic outcome for those participants receiving treatment for the entire 30 month follow-up period, compared with those participants receiving tafamidis for only the last 12 months of this period. This highlights the importance of early diagnosis and initiation of treatment as soon as possible.

- TTR amyloid polyneuropathy is an ultra-orphan disease with estimated world-wide patient population of <10,000. There is a serious unmet medical need for an effective pharmacologic therapy, as the only currently available treatment is liver transplantation. However, liver transplantation is insufficient given the shortage of available organs, first-year mortality rates of approximately 10%, long-term morbidity due to chronic immunosuppression and progression of cardiomyopathy post-transplantation. In addition, for those patients who are not liver transplant candidates, or unable to find a suitable match, there are no available treatments. Thus, tafamidis offers ATTR-PN patients a viable pharmacologic treatment that preserves neurologic function, nutritional status and quality of life. The effects on overall survival will be determined in the post-marketing setting.

2.3.2. Risks

Safety issues that have been identified as risks or considered as potential risks associated with tafamidis treatment are discussed below:

- Identified Adverse Drug Reactions (ADRs): participants in the tafamidis treatment arm of the placebo-controlled study Fx-005 experienced certain adverse events at a higher rate than placebo-treated participants. Based on review and all available AE data for ATTR-PN participants receiving 20 mg of tafamidis meglumine administered daily for an average of 538 days (n = 127), and taking into account other factors such as the mechanism of action of tafamidis, the known symptoms of underlying TTR amyloidosis disease, and the temporality of the adverse event to the administration of tafamidis, adverse drug reactions (ie, adverse events for which there is a reason to conclude that tafamidis caused the event) were determined to be: urinary tract infection, diarrhea, upper abdominal pain, and vaginal infection.

- Theoretical/Potential Risks:

  - Liver enzyme elevations: A participant in Study Fx-005 (01-062) was observed to have an increase in liver enzymes (AST(aspartate aminotransferase), ALT(alanine aminotransferase), GGT(gamma-glutamyl transferase)) following 18 months of treatment with tafamidis meglumine 20 mg daily. The liver function abnormalities improved despite continuation of tafamidis. Review of the case, including liver biopsy findings, by an independent expert determined that drug-induced liver injury was unlikely.

    However, given the importance of this potential safety risk, liver function in participants taking tafamidis will continue to be assessed and monitored in clinical trials. Spontaneous reports consistent with possible drug induced liver injury will be identified for specific data collection using a hepatotoxicity data capture aid questionnaire(refer to Appendix 6 for liver safety: Suggested Actions and Follow-up Assessments).

  - Hypersensitivity: A hypersensitivity reaction and a case of urticaria occurred in the clinical trials with tafamidis - neither case provided definitive evidence of tafamidis hypersensitivity. However, due to the uncertainty around causality from these reports and the potential putative role of the acyl glucuronide metabolite of tafamidis in hypersensitivity reactions, spontaneous reports consistent with hypersensitivity and/or skin reactions will be identified for specific data collection using an Allergic reactions, Hypersensitivity, Skin reaction data capture aid questionnaire.

  - Reproductive toxicity: Due to preclinical rabbit developmental toxicity findings, the relative lack of data on pregnant women exposed to tafamidis, and information on human reproductive toxicity, all women of childbearing potential should use appropriate contraception when taking tafamidis. To collect information about

women who inadvertently become pregnant while taking tafamidis, the TESPO (Tafamidis Enhanced Surveillance of Pregnancy Outcomes) program will be in place to extend collection of routine post-natal safety information collection to 12 months post birth with questions regarding developmental progression.

- Changes in thyroid function, particularly in pregnant women. Due to the theoretical risk of thyroid function abnormalities related to displacement of thyroxine from the thyroxine binding site on the transthyretin tetramer, and given the increased risk of thyroid dysfunction during pregnancy and potential negative impact to the fetus, a thyroid dysfunction data capture aid will be incorporated into routine pharmacovigilance activities for adverse event reports consistent with thyroid dysfunction. In addition, information about thyroid function will be requested in cases of exposure during pregnancy.

- Participants enrolled in the clinical studies were intended to represent the general population of patients with the disease. As ATTR-PN is endemic to certain locales (eg, Portugal), enrollment of participants from these centers of high disease prevalence was performed. The inclusion/exclusion criteria were generally unrestrictive; however, criteria did preclude participants with more advanced stage of disease from enrollment. Outcomes from the development program can be extrapolated to the general population with ATTR-PN with early to mid-stage disease. The effect of tafamidis in patients with severe disease is not known.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Estimands	Endpoints
Primary:		
To evaluate the effect of tafamidis meglumine on clinical efficacy in ATTR-PN participants.	Descriptive statistics of the NIS-LL change from baseline at Week 72 (Month 18), regardless of whether or not participant continues with/adheres to treatment	Change from baseline NIS-LL at Week 72 (Month 18)
Secondary:		
To evaluate the efficacy, safety, tolerability, and pharmacodynamics of tafamidis meglumine in ATTR-PN participants.	Descriptive statistics of the secondary endpoints in ATTR-PN participants, regardless of whether or not participant continues with/adheres to treatment.	Efficacy: Change from baseline at follow-up visit on the following scales: • NIS-LL at other visits than Week 72 • TQOL score and 5 domains as measured by the Norfolk QOL - Diabetic Neuropathy (Norfolk QOL-DN); • Modified Body Mass Index (mBMI); • 36-item short form (SF-36); • EQ-5D-5L Index Score. Safety: Adverse events, vital signs (temperature, blood pressure, pulse rate, and respiratory rate), ECGs, ECHO, clinical laboratory evaluations. Pharmacodynamics: TTR stabilization and TTR concentration at Day 1 (baseline),

		Week 8, Week 12, Week 24, Week 48 and Week 72.

However, when the investigator has judged the SAE (serious adverse event) to have a causal relationship with the investigational product, the investigator must additionally repo1t the event to Pfizer Safety as described in the Adverse Event Repo1ting section, even if that event is a component of the endpoint.

4. STUDY DESIGN

4.1. Overall Design

This is a single-rum, open-label, multicenter study designed to evaluate the efficacy, safety, tolerability and phrumacodynamics oftafamiclis meglumine in ATTR-PN pruticipants in China.

Approximately 10-15 participants will be enrolled. CCI [redacted] All emolled pruticipants will receive oral tafamidis meglumine 20 mg soft capsules once daily struting on Day 1. At Day 1, Week 24, Week 48 and Week 72 (or Early Study Discontinuation), NIS-LL testing will be perfo1med for each pruticipant to dete1mine the change from baseline. At Day **1** (Baseline), Week 8, Week 12, Week 24, Week 48 and Week 72 (or Eru·ly Study Discontinuation), blood samples will be collected from each pruticipant to dete1mine TTR stabilization and TTR concentration.

Before engaging in any study procedme, each pruticipant must sign and date an info1med consent fo1m. Paiticipants will be evaluated for study eligibility dming the screening period between Days -30 and Day 0. Screening laborato1y evaluations must be completed within 3 days before Baseline (Day **1)** in order for results to be available and reviewed before study emollment.

Paiticipants who are dete1mined to be eligible, based on screening assessments, will be emolled in the study. After completion of Screening and Baseline assessments, participants will sta1t study medication on Day **1.**

Interventional product should be taken at the same time each day throughout the treatment period.

Clinical visits will be scheduled at Baseline (Day **1)** and at Week 4, Week 8, Week 12, Week 24, Week 48, Week 60 and Week 72 (or Eru·ly Study Discontinuation). At Week 36 and Week 60 site visit, assessment of adverse events, safety related lab testings, concomitant medications and investigational product compliance will be scheduled. Eve1y 6 weeks (with a window of ±7 days) telephone contacts will be made dming visits in which no investigative site visits are scheduled for assessment of adverse events, concomitant medications and investigational product compliance (between Week 12 and 24, Week 24 and 36, Week 36 and 48, Week 48 and 60, and between Week 60 and 72).

Efficacy assessments to be perfonned during the study include NIS-LL (Neuropathy Impai.J.ment Score-Lower Limb), Norfolk QOL-DN (Norfolk Quality of Life - Diabetic Neuropathy), mBMI, SF-36 (36-Item Survey) and EQ-5D-5L (EuroQoL-5 Dimensions 5 Levels). NIS-LL testing is perfo1med 2 times at least 24 hours apart within a I-week period by the same neurologist before and/or at the baseline visit. Both evaluations are completed prior to study medication administration at baseline visit.

Safety assessments to be perfonned during the study includemeasurement of vital signs, clinical laborat01y evaluations, including hematology, coagulation panel, and sernm chemistiy, ECG (electi·ocardiogram), ECHO (Echogram) and monitoring of adverse events.

4.2. Scientific Rationale for Study Design

In August 2018, the Notice on Soliciting Opinions on List of New Drngs with Urgent Clinical Need Marketed Overseas announced that tafamidis for ATTR-PN was included in the NMPA List of 48 products for which there was an urgent clinical need in China.

CCI [redacted] This study is desi~ned to be a single arm study to evaluate the clinical efficacy with NIS-LL change from baseline as well as tafamidis meglumine efficacy based on other parameters, safety, tolerability and pharmacodynamics in A1TR--PN paiiicipants in China CCI [redacted]

Considering the exti-emely low revalence of ATTR-PN in China as a rai·e disease, the proposed sample size for the study may already be ve1y challenging for recrnitment. T 1e estnnahon to recrn1t approximatelyl0-15 patiicipants is based on the practical li.J.nitation of patients in China. The original proposed 6 months ti·eatlnent duration is based on the previous experience on license renewal timeline- [redacted] and 6 months is enouoh for collectin_ TTR stabilization data, safet, and tolerability data. CCI [redacted] t e ti·eatlnent and observation duration is extended to 18 months (Week 72) in protocol amendment 3.

4.3. Justification for Dose

The proposed dosing regimen and administi·ation in this study is 20 mg soft tafainidis meglumine capsule (containing 12.2 mg oftafamidis free-acid) administered orally once daily, with or without food, consistent with the approved label in China.

The approved therapeutic indication for tafamidis meglumine in China is same as is cmTently approved in the EU: "Treatment of ti·ansthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment." Tafamidis meglumine soft capsule is also approved in Japan i.J.12013 for "delay of peripheral neurologic impai1ment in patients with ti·ansthyretin familial amyloid polyneuropathy (TTR-FAP(Transthyretin Familial Amyloid Pol euro ath "with the same dosing recommendation 20 m_, orall,, dail,;. CCI [redacted]

CCI [redacted][18] The conclusion of the report is "Study of adverse reactions and infections etc. during the survey unit period revealed no particular problematic characteristic issues in terms of the safety of VYNDAQEL. Therefore, it was concluded that no further safety assurance measures need be adopted at this time."

The efficacy and safety of once daily 20 mg tafamidis meglumine for the treatment of ATTR-PN was demonstrated in participants with a documented Val30Met TTR variant in the randomized placebo-controlled clinical trial B3461020 (Fx-005) and in the subsequent long term extension study B3461023. Additional supportive data were provided by an ongoing, non-interventional study (Transthyretin-Associated Amyloidosis Outcomes Survey [THAOS]) (Study B3461001), independent analysis of data collected in Portuguese specialized centers, and analyses of data from participants with non-Val30Met mutation participating in study B3461023 or B3461022 (Fx1A-201).

This approved dosing regimen in China (the one in this study), is the same as the one approved in EU and Japan, is also supported by following data from Asian participant, primarily from Japanese, when comparing to data from Western participants as appropriate.

- Study B3461009 is a Phase 1, single center, double-blinded (sponsor-open), placebo controlled parallel study in healthy Japanese and Western volunteers. Each participant was randomly assigned to a single treatment of either tafamidis meglumine 20 mg Phase 2/3 capsule, tafamidis meglumine 40 mg (2 x 20 mg) Phase 2/3 capsules, or placebo capsule in a 3:3:1 fashion, in the fasted state. Serial plasma samples were collected for 168 hours post dose. Mean PK parameters were similar between Japanese and Western participants (please see Table 14.4.3.1 of the B3461009 Report Body). Percent stabilization at T_{max} (time of maximum observed concentration) and 24 hours post-dose of tafamidis meglumine 20 mg or 40 mg was similar between Japanese and Western participants (Figure 4 of B3461009 Report Body).

- Study B3461010 is an uncontrolled, open-label Phase 3 study with the primary objective of determining TTR stabilization at steady-state, as measured in Japanese participants with ATTR-PN following oral tafamidis meglumine 20 mg soft capsules once daily. The study enrolled 10 participants; 7 completed study treatment and 3 discontinued. All participants were treated with 20 mg tafamidis meglumine (orally, once daily). The TTR genotypes were Val30Met in 9 participants and non-Val30Met (Ser77Tyr) in 1 participant. All participantsachieved TTR stabilization (the percent stabilization was equal to or greater than 32%) at Week 8, Week 26, and 9 of 10 participants (90.0%) at Week 52 and 8 of 10 participants (80.0%) at Week 78 achieved TTR stabilization. Data from this study contributed to the population PK (pharmacokinetic(s)) analyses and the TTR stabilization analyses summarized following this.

- In order to examine the effect of certain intrinsic factors including age, gender, race, health status, and renal function on the PK of tafamidis, a population PK analysis was conducted with analysis dataset consisted of 13,123 observations from 760 participants (333 healthy participants, 292 ATTR-CM participants, and 135 ATTR-PN participants). Of those observations, a total of 11,472 were used in the population PK analysis after consideration of exclusions due to data exclusion criteria and observations below the limit of quantification. The study population consisted of 639 males and 121 females with a median age of 49.5 years (range 18 88 years) and a median weight of 76 kg (range 32 – 133.8 kg). There were 584 White, 61 Black, 69 Asian, 45 Other, and 1 of unknown race. The median value for creatinine clearance was 93.7 mL/min (range 17.4 – 220.6 mL/min). Nine moderate and 9 mild hepatic impaired participants from the Phase 1 hepatic impairment study B3461016 (Fx1A-105) were included in the hepatically impaired group. Results from this analysis showed that no dosage adjustment is necessary with tafamidis for intrinsic or extrinsic factors, including gender, race, age, nor for participants with renal impairment or mild and moderate hepatic impairment. No data are available in participants with severe hepatic impairment. The results support tafamidis meglumine 20 mg once-daily oral dosing.

- Population pharmacodynamics analyses (% TTR stabilization relative to tafamidis: TTR stoichiometry) were conducted using pooled data from 11 different clinical studies in which TTR stabilization was measured. In this analysis there were 5.5% (36/660) Japanese participants. No clinically meaningful impact of ethnicity (Japanese vs non-Japanese) was noted on the exposure-response relationship.

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 the last visit.

The end of the study is defined as the date of the last visit of the last participant in the study.

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:

1. Male or female participants between the ages of 18 and 80 years.

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

Type of Participant and Disease Characteristics:

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

3. Participants have amyloid documented by biopsy in accordance with institutional site standard of care (Biopsy must have been performed within 5 years of enrollment).

4. Participants must have a TTR mutation that is associated with ATTR-PN. (See Section 8.2.6.3 for further details).

5. Participants have peripheral and/or autonomic neuropathy with a Karnofsky Performance Status ≥50 (refer to Appendix 5).

6. Stages of disease according to symptom severity-stage I.

Informed Consent:

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

3. Use of diflunisal, tauroursodeoxycholate, doxycycline, inotersen, patisiran or any other TTR stabilizing agent, or experimental interventions for familial amyloidosis within 30 days prior to the study entry and/or during study participation. Participants who are taking or who have previously taken tafamidis.

Prior/Concurrent Clinical Study Experience:

4. Previous administration with an investigational drug within 30 days or 5 half-lives preceding the first dose of investigational product used in this study (whichever is longer).

Diagnostic Assessments:

5. Participant has primary (light chain) or secondary amyloidosis.

6. If female, participant is pregnant or breast feeding, or plans to be pregnant or breast feeding in the next 18 months.

7. Participant has received prior liver or any other organ except cornea transplantation.

8. Participant requires significant assistance with ambulation or is wheel chair bound.

9. Participants with positive results for hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV), and/or human immunodeficiency virus (HIV).

10. Participant has liver function test abnormalities: alanine transaminases (ALT) and/or aspartate transaminases (AST) >2 times upper limit of normal (ULN) that in the medical judgment of the investigator are due to reduced liver function or active liver disease.

11. Participants with cardiomyopathy specific TTR mutations (eg, Val122Ile, Leu111Met, Ile68Leu).

12. Participant has a co-morbidity anticipated to limit survival to less than 18 months.

13. Participant has other causes of sensorimotor neuropathy (B12 deficiency, Diabetes Mellitus, HIV treated with retroviral medications, thyroid disorders, alcohol abuse, Fabry disease, Lyme disease, sarcoidosis, Sjogren's Syndrome, Systemic Lupus Erythematosus, alcohol dependency, celiac disease, Chronic Inflammatory Demyelinating Polyneuropathy, and chronic inflammatory diseases).

Other Exclusions:

14. 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. Activity

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

5.3.2. 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 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.

Participants need to affirm that they meet the criteria for correct use of at least 2 of the selected methods of contraception. In this study, female participants who are of childbearing potential may receive tafamidis, which has been associated with teratogenic risk. All female participants who are of childbearing potential and, in the opinion of the investigator, are sexually active and at risk for pregnancy must agree to use with their partner(s) 2 methods of highly effective contraception must be used throughout the study and continued for 28 days after the last dose.

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

1. Established use of oral, inserted, injected, implanted or transdermal hormonal methods of contraception are allowed provided the participant plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed intrauterine device (IUD) or intrauterine hormone-releasing system (IUS).

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

4. Male sterilization with absence of sperm in the postvasectomy ejaculate.

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

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. 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 30 days, the individual inclusion/exclusion criteria may need repeating according to the nature of the medical event and clinical judgement of the investigator.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened. For individuals whose eligibility assessment has been impacted due to public emergencies (including COVID-19), please refer to Section 10.9.1.

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.

6.1. Study Intervention(s) Administered

Intervention Name	Tafamidis meglumine PF-06291826
ARM Name	N/A
Type	Drug
Dose Formulation	Tafamidis meglumine soft capsule 20 mg.
Unit Dose Strength(s)	Tafamidis meglumine soft capsule 20 mg.
Dosage Level(s)	20 mg once daily.

Route of Administration	Oral
Investigational Medicinal Product (IMP) and Noninvestigational Medicinal Product (NIMP)	IMP
Sourcing	Provided centrally by the sponsor as soft capsules containing tafamidis meglumine 20 mg. Refer to the IP manual.
Packaging and Labeling	Study intervention will be provided in packs of 30 x 1 soft capsules. Each pack will be labeled as per country requirement. The product will be provided as open label.

6.1.1. Administration

All enrolled participants will receive a once-daily oral dose of tafamidis meglumine 20 mg in a soft capsule formulation. Each participant will receive the first dose of study medication on Day 1 at site during clinic visit.

Participants will self-administer investigational product at home except Day 1 (baseline). Investigational product is to be taken by mouth, with water. Participants will be instructed to take investigational product at the same time each day throughout the treatment period.

Participants will swallow the investigational product whole, and will not manipulate or chew the investigational product prior to swallowing.

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. All empty containers (as appropriate) and unused products must be taken to the investigator by the participant at every visit and at the end of the study.

4. Further guidance and information for the final disposition of unused study interventions are provided in the Investigational product (IP) manual.

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 IP manual.

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.

Additional details about accountability, storage, destruction, and excursion reporting can be found in the IP manual.

6.2.1. Preparation and Dispensing

The investigational product will be dispensed by pharmacist/site staff manually at each visit from Day 1 onwards until end of trial (EOT) according to the IP manual. A qualified staff member will dispense the investigational product, in quantities appropriate for the study visit schedule. The participant/caregiver should be instructed to maintain the product in the container(s) provided throughout the course of dosing and take the container(s) to the site at the next study visit.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Investigational Product

This is an open-label, single arm study; potential bias will be reduced by the following steps: data review committee to evaluate all the data collected. The investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

Investigational product will be dispensed at the study visits summarized in the SoA.

6.4. Study Intervention Compliance

All investigational product will be self-administered by the study participants at home except taking it at site during clinic visit on Day 1 (baseline). Treatment compliance will be determined through capsule counting procedures at followup visits and participants-physician interviews during the scheduled study visits. Compliance will be monitored and recorded in Drug Accountability Form and each participant's CRF(case report form). Additionally, interventional product accountability audits will be performed by the study monitor during routine monitoring visits.

6.5. Concomitant Therapy

6.5.1. Permitted Medicine

Over-the-counter (OTC) medications may be taken after study medication administration for the management of a self-limiting indication (eg, acetaminophen for headache) at the investigator's discretion. The use of concomitant OTC medications must be approved by the investigator before administration. All prescription medications must be approved by the investigator throughout the treatment period of the study. All participants will be instructed regarding the importance of consulting with the investigator before taking any medication during the study. Use of concomitant drugs with a narrow therapeutic window, eg, warfarin and digoxin, should be done with caution. Monitoring of adverse effects will be performed.

All medication taken by the participant during the study must be recorded in the participant's eCRF. 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.

6.5.2. Excluded Medicine, Treatment and Substances

The following medications and substances are prohibited during the study, as specified below:

- Any investigational intervention within 30 days before Day 1 (Baseline) and during the study participation.
- Chronic use of non-protocol approved non-steroidal anti-inflammatory drugs (NSAIDs), defined as greater than 4 times/month. The following NSAID are

allowed: acetylsalicylic acid, etodolac, ibuprofen, indomethacin, ketoprofen, nabumetone, naproxen, nimesulide, piroxicam, and sulindac. Topical ophthalmic NSAIDs administered while the participant's nasal punctum is occluded are also permitted. All other NSAIDs are prohibited.Use of diflunisal, tauroursodeoxycholate, doxycycline, inotersen or patisiran or any other TTR stabilizing agent within 30 days prior to the study entry and/or during study participation is prohibited.

- Liver or any other organ except cornea transplantation is prohibited during study participation. Participants undergoing liver or any other organ except cornea transplantation will be withdrawn from the study.

- Drugs known to affect autonomic function and impact orthostatic blood pressure measurements.

- Anticholinergics (eg, tricyclic antidepressants, antispasmodics, antihistamines, over-the counter cold remedies):

    - Participants who are stable on anticholinergics at study start should try to maintain the dose and frequency throughout the study.

- Sympathomimetics, diuretics and alpha blockers (including those for benign prostate hyperplasia):

    - Participants who are stable on sympathomimetics, diuretics and alpha blockers at study start should try to maintain the dose and frequency throughout the study;

    - Any sympathomimetics, diuretics and alpha blockers started after the screening assessments must be discontinued for 72 hours prior to conducting any clinical assessments of orthostatic blood pressure, provided there is no safety risk to the participant. A list of prohibited medications as examples will be provided in the Study manual.

- Nicotine, caffeine and alcohol are not permitted for 3 hours prior to orthostatic blood pressure measurements.

6.5.3. Rescue Medicine

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

6.6. Dose Modification

No dose modification is required based on age and gender.

6.7. Intervention After the End of the Study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention include the following:

- Withdrawal of consent;
- Pregnancy;
- Protocol noncompliance;
- Liver or other organ except cornea transplantation;
- Unexpected allergic reaction;
- Serious disease;
- Serious and/or intolerable adverse events;
- Others, which investigators decide not to continue study.

Note that discontinuation of investigational product does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated. 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.

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.

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 study procedures;
- Lost to follow-up;
- Death;
- Study terminated by sponsor.

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

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.

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 followup, 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 followup, 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 Followup

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. 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.

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 TTR stabilization and TTR concentrationshould be obtained within the specified time windows if applicable.
5. All the assessments and procedures at baseline visit in the SoA should be completed prior to the investigational product administration on Day 1.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

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.

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

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.

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

The total blood sampling volume for individual participants in this study is approximately 200-250 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 300 mL, and 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

8.1.1. Neuropathy Impairment Score-Lower Limb (NIS-LL)

The neurologic functioning will be evaluated using the Neuropathy Impairment Score (NIS) scale. NIS scale will provide a single score of total body neuropathic deficits and total body subset scores for cranial nerves, muscle weakness, reflexes, and sensation. The NIS scoring categories are cranial nerves, muscle weakness, reflexes, and sensation. Each item is scored separately for left and right.

Only a subset of the NIS scale focusing on the lower limbs (NIS-LL) will be performed to provide a single score of lower limb neuropathic deficits and lower limb subset scores for muscle weakness, reflexes, and sensation in great toe. The subset for the lower limbs (NIS-LL) includes muscle weakness (sum of Items 1-8), reflexes (sum of Items 9 and 10), sensation in great toe (sum of Items 11-14). The total NIS-LL score will be calculated as the sum of the subset scores. During this study, NIS-LL assessments will be performed 2 times at least 24 hours apart within a 1-week period at times specified in the NIS-LL assessments at baseline are completed prior to study medication administration. The average of the 2 NIS-LL scores will be used for analysis. Each participant's NIS-LL testing is to be performed by the same neurologist throughout the course of the study.

Components of cranial nerves, muscle weakness are scored to eight levels:

0 = Normal
1 = 25% Weak
2 = 50% Weak
3 = 75% Weak
3.25 = Move against gravity
3.5 = Movement, gravity eliminated
3.75 = Muscle flicker, no movement
4 = Paralysis

Components of reflexes and sensation (touch pressure, pin-prick, vibration, and joint position) in index finger and great toe are scored 0 = normal, 1= decreased, or 2 = absent.

The neurologists involved in NIS scoring must undergo training sessions that will illustrate the method to normalize the data generated by the physician examination. In addition, all neurologists will receive a NIS training video prepared specifically for this study(refer to Appendix 8 for details).

8.1.2. Norfolk QOL-DN

Quality of Life (QOL) will be assessed using the Norfolk QOL-DN, a tool which was developed to capture participant-reported aspects of neuropathy, particularly when the participant base is comprised of participants with polyneuropathy and somatic and autonomic symptoms. The Norfolk QOL-DN has been used to evaluate several diabetic neuropathy drugs in clinical trials. The developers showed in a study population in Germany with 5 stages of neuropathy severity according to the criteria of Dyck[19] that Norfolk QOL-DN was able to discriminate the presence of neuropathy and distinguish the stages within the population.[20]

The Norfolk QOL-DN is a self-administered questionnaire, designed to capture and quantify the impact of neuropathy on the quality of life of individual participants with neuropathy. The 35 scored questions are numbered items that comprise the entire scale, and they are arranged thematically so that the wording of the questions and the type of response is grouped together. However, the content and topic of each individual question concerns particular functions or symptoms that are related to the following themes:

- Total Quality of Life Score;
- Physical Functioning/Large Fiber Neuropathy;
- Activities of Daily Living (ADLs);
- Symptoms;
- Small Fiber Neuropathy;

- Autonomic Neuropathy.

Quality of Life (QOL) will be assessed using the Norfolk QOL-DN at times specified in theSoA.

Additional details on the content of the Norfolk QOL-DN and how it is scored are contained in a stand alone document.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

A complete physical examination will include assessments of the general appearance, head and neck, eyes, ears, nose, throat, genitourinary, endocrine, skin, musculoskeletal, immunologic/allergies, hematologic/lymphatic, cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded.

An abbreviated physical examination will include assessments of the general appearance, cardiovascular, respiratory and gastrointestinal system.

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

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.3.1 to 8.3.3.

8.2.2. Vital Signs

Vital signs will be recorded at times specified in the SoA.

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

8.2.3. Electrocardiograms

12-Lead ECGs should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTc intervals and QRS complex. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position.

If a postdose QTcF interval remains ≥30 msec from the baseline **and** is >450 msec; or b) an absolute QT or QTcF value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator), or QTcF intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF intervals do not return to less than the criterion listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

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 (generally QTcB), 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. 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.

The values of laboratory tests obtained on Day 1 will be considered as baseline assessment.

All blood samples for laboratory safety tests will be collected in the morning prior to administration of study medication. All values obtained during the study are to be recorded in the eCRF.

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 4 weeks 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 such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

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.

8.2.5. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP (woman of childbearing potential)at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior the participant's receiving the investigational product. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and 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. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.2.6. Other Assessment

8.2.6.1. Medical History

A complete medical history is to be documented for all participants during the screening period.

8.2.6.2. Biopsy Documentation of Amyloid

Nerve, rectal, fat pad, skin tissue, salivary gland samples or other acceptable tissue must be tested by the investigational site as per the site's standard of care for amyloid biopsy using Congo red staining to confirm the presence of amyloid. Stained tissue will be viewed under polarized light used to demonstrate amyloid characteristic 'apple-green' birefringence or other analysis can be utilized to confirm the deposit of amyloid. It is possible that the participant's amyloid biopsy may have been performed before the Screening visit outside the auspices of this study.

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.

8.2.6.3. TTR Genotyping

At the time of Screening examination, a serum sample will be obtained to analyze complete TTR sequencing at the investigational site by institutional site standard of care. If TTR

genotyping showing Val30Met or non Val30Met has been performed within last 5 years, a participant can start to be dosed.

8.2.6.4. Echocardiograms

Echocardiography (2D Doppler) will be performed for all participants at timepoint on the SoA. 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.

The following parameters will be included in the assessment:

1. Interventricular septal wall thickness (mm);
2. Left ventricle posterior wall thickness (mm);
3. Left ventricular ejection fraction (%);
4. Left ventricular stroke volume (mL);
5. Fractional shortening (%);
6. Left atrial diameter, anterior-posterior (mm);
7. Left atrial diameter, medio-lateral (mm);
8. Left atrial diameter, superior-inferior (mm);
9. Left ventricular end systolic diameter (mm);
10. Left ventricular end systolic volume (mL);
11. Left ventricular end diastolic diameter (mm);
12. Left ventricular end diastolic volume (mL);
13. Left ventricular mass (g);
14. E/A(E peak/A peak) Ratio.

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

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

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the Investigator or other healthcare providers (clinical signs, test results, etc.).

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 it meets the criteria for classification as an SAE or that caused the participant to discontinue the study intervention (see Section 7.1).

During the active collection period as described in Section 8.3.1, 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 investigational product), through and including a minimum of 28 calendar days 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.

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 permanently 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 information on 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. Followup 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. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure, occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include exposure during pregnancy, exposure during breastfeeding, and occupational exposure.

Any such exposure to the study intervention under study 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 EDP:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion, inhalation or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion, inhalation or skin contact, 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 ingestion, 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

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information about the occupational exposure 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 must be maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events

Not applicable.

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

The following disease-related event (DREs) is common in participants with ATTR-PN and can be serious/life threatening:

- Death.

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of an SAE. These events will be recorded on the corresponding CRF page in the participant's CRF within 24 hours.

AEs reported from studies associated with hospitalization or prolongations of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Hospitalization does not include the following:

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

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

1. Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment lab abnormality);
2. Social admission (eg, participanthas no place to sleep);
3. Administrative admission (eg, for yearly physical exam);

4. Protocol-specified admission during a study (eg, for a procedure required by the study protocol);

5. Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);

6. Hospitalization for observation without a medical AE;

7. Pre-planned treatments or surgical procedures should be noted in the Baseline documentation for the entire protocol and/or for the individual participant.

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

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a DRE):

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

  OR

- The investigator considers that there is a reasonable possibility that the event was related to study intervention.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety only if associated with an SAE.

8.3.9. Medical 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 meglumine greater than 20 mg within a 24-hour time period will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.

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 meglumine (whichever is longer).

2. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

3. Overdose is reportable to Safety **only when associated with an SAE.**

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

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters of TTR stabilization and TTR concentrations are evaluated as secondary endpoints in this study.

One (1) dipotassium ethylenediaminetetraacetic acid (K2 EDTA) blood sample of approximately 10 mL (with exception of an additional 10 mL of K2 EDTA blood sample taken at the pre-dose blood sample only on Day 1 (Baseline) for method development and validation) will be collected for measurement of TTR stabilization and TTR concentrations pre-dose during the clinic visit on Day 1 (Baseline), and during the clinic visits at Week 8, Week 12, Week 24, Week 48, and Week 72 (or End of Treatment/Early Study Discontinuation), please refer to SoA for details. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24 hour clock time) of each sample will be recorded. Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.

The samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the 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. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.8. Genetics

8.8.1. Specified Genetics

Genetics (specified analyses) are not evaluated in this study.

8.9. Biomarkers

Biomarkers are not evaluated in this study.

8.10. Health Economics

SF-36 and EQ-5D-5L will be measured in this study.

8.10.1. 36-Item Short Form Survey (SF-36)

The SF-36 includes 36 items covering 8 domains: physical function (PF, 10 items), role-physical (RP, 4 items), bodily pain (2 items), general health (GH, 5 items), vitality (VT, 4 items), social function (SF, 2 items), role-emotional (RE, 3 items), and mental health (MH, 5 items).

The health-related quality of life will be evaluated with Chinese version of 36 Item Short Form Survey (SF-36), which is regarded as a measurement tool by which to evaluate quality of life, and has a wide range of applications. See the SoA for time points when this will be performed (refer to a stand alone document for details).

8.10.2. 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 health-related quality of life will be evaluated with a standardized instrument EQ-5D-5L (Chinese version) that can be used in a wide range of health conditions and treatments. See the SoA for time points when this will be performed (refer to a stand alone document for details).

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.

9.1.1. Estimands

9.1.1.1. Primary Estimand

The primary estimand will be the descriptive statistics of the primary endpoint, change from baseline NIS-LL at Week 72 (Month 18), regardless of whether or not participant continues with/adheres to treatment. This includes all observations collected after treatment discontinuation or non-adherence to treatment.

9.1.1.2. Secondary Estimands

The secondary estimands will be the descriptive statistics of the corresponding secondary endpoints in ATTR-PN participants, regardless of whether or not participant continues with/adheres to treatment.

9.2. Sample Size Determination

Due to the practical limitation of eligible patients, around 10-15 participants will be enrolled in this study.

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 meglumine soft capsule 20 mg.
Safety	The same as above efficacy population.
Pharmacodynamic	All participants who have at least 1 assessment 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.

9.4.1. Efficacy Analyses

All efficacy analyses will be performed on the efficacy population. Both baseline and change from baseline efficacy measures will be summarized descriptively by visit. Baseline for any endpoints is defined as the last measurement prior to dosing on Day 1 of the study, unless otherwise specified. Change from baseline value is calculated by subtracting the baseline value from follow up visit value.

9.4.1.1. Neuropathy Impairment Score-Lower Limb (NIS-LL)

NIS-LL testing is performed 2 times at each visit as per the SoA. The average value of the 2 scores will be used for the analysis.

NIS-LL will be utilized to calculate a total neuropathic deficit score for the lower limbs. In addition, subset scores for the lower limbs: muscle weakness (sum of Items 1-8), reflexes (sum of Items 9 and 10), sensation in great toe (sum of Items 11-14) will be calculated. The total NIS-LL will be calculated as the sum of the subset scores.

9.4.1.2. Modified BMI(body mass index)

The mBMI, calculated by multiplying the BMI (kg/height in m^2) by serum albumin level (g/L), will be evaluated.

9.4.1.3. Norfolk QOL-DN

The 35 individual questions are grouped into total score and 5 domains and will be calculated as follows:

1 Total QOL; sum of items 1-35

1 Physical Functioning/Large Fiber; sum of items 8, 11, 13-15, 24, 27-35

1 Activities of Daily Living (ADLs); sum of items 12, 22, 23, 25, 26

1 Symptoms; sum of items 1-7, 9

1 Small Fiber; sum of items 10, 16, 17, 18

1 Autonomic; sum of items 19, 20, 21

If missing questions occurs, the missing score will be imputed as the mean of the non-missing questions within the domain for that visit as long as at least 60% of the items within the domain have a non-missing response. The domain score will then be the sum of the non-missing and imputed questions. If all 35 questions are non-missing or imputed as defined above, then the total QOL will be calculated as the sum of the non-missing items and the imputed values. If questions could not be imputed as defined above due to less than 60% of responses in a domain; however, at least 60% of the total questions are either non-missing or imputed, then the total QOL will be calculated as the mean of the non-missing and imputed questions times 35. If greater than 40% of the items in a domain or Total QOL are missing, then the domain is deemed missing.

9.4.2. Safety Analyses

All safety analyses will be performed on the safety population. Safety and tolerability data will be summarized descriptively in tabular or graphical format.

- The incidence of all adverse event and all laboratory test abnormalities will be tabulated.

- Effects of tafamidis on temperature, blood pressure, pulse rate, respiratory rate, QT/QTc will be evaluated for baseline and change from baseline values at each visit.

9.4.3. 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.

9.4.3.1. 36-item-Short Form (SF-36) Score

The SF-36 includes 36 items covering 8 domains: physical function (PF, 10 items), rolephysical (RP, 4 items), bodily pain (2 items), general health (GH, 5 items), vitality (VT, 4 items), social function (SF, 2 items), role-emotional (RE, 3 items), and mental health

(MH, 5 items). Scoring method: According to the different weights attributed to each item, the SF36 scoring method calculates the sum of the integrals of each item in each dimension, obtains the integrals of eight dimensions. The Physical Component Summary (PCS) is assessed by grouping all physical components (PF, RP, BP, and GH) together; similarly, the Mental Component Summary (MCS) encompasses mental components (VT, SF, RE, and MH), and then converts the integrals into the final score ranging from 0 to 100. High scores in each dimension and high overall scores indicate a better quality of life.

9.4.3.2. EQ-5D-5L Index Score

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 participant 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 participant'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 participant'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).

9.4.4. Pharmacodynamics: 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 equal to or greater than 32%.

All pharmacodynamic analyses will be performed on the pharmacodynamic population. TTR concentration and percent stabilization will be summarized descriptively, as continuous measures, by visit, regardless of whether or not participant continues with/adhere to treatment. 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, by visit, regardless of whether or not participant continues with/adhere to treatment.

9.5. Interim Analyses

No formal interim analysis will be conducted for this study. As this is an open label study, the sponsor may conduct reviews of the data during the course of the study for the purpose of safety assessment or supporting clinical development decisions.

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 investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study 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 or 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 or 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 30 days from the previous ICD signature date.

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(clinical study report) 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 source document agreement.

10.1.8. Study and Site Closure

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

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

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. 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 ICH GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.
- If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s)

used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

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

10.1.9. Publication Policy

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 supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with an Emergency Contact Card (ECC) at the time of informed consent. The ECCcontains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, (c) site emergency

phone number active 24 hours/day, 7 days per week, and (d) Pfizer Call Center number.The ECC is intended to augment, but not replace, the established communication pathways between the investigator site and the study team. The ECC is to be used by healthcare professionals not involved in the research study only, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number should only be used when the investigator and site staff cannot be reached. The Pfizer Call Center number is not intended for use by the participant directly, 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 2. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN/Urea and creatinine Glucose (fasting) Ca++ Na+, K+, Cl- Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Gamma glutamyl transferase (GGT) Uric acid Albumin Total protein Total Cholesterol Inorganic Phosphorous Globulin Thyroid-stimulating hormone (TSH) Total thyroxine (T4) Free T4 NT-pro-BNP Troponin I/Troponin T	Protein Nitrites Leukocytes (qualitative) Occult blood Microscopy and culture[a]	FSH[b] Urine pregnancy testing Serum pregnancy testing Coagulation Panel (PT, PTT, and INR) Retinol-binding protein HBsAg,[c] HIV antibody,[c] HCV antibodies[c]

Abbreviations: Abs = absolute; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; Ca = Calcium; Cl = Chlorine; CO_2 = carbon dioxide; FSH = follicle-stimulating hormone; GGT: Gamma glutamyl transferase; Hb = Hemoglobin; HBsAg = Hepatitis B surface antigen; HCV = Hepatitis C antibody; HIV = human immunodeficiency virus; INR = international normalized ratio; K = potassium; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; Na = sodium; NT-pro-BNP = N-terminal B-type natriuretic peptide; PT = prothrombin time; PTT = Partial Thromboplastin Time; qual = qualitative; RBC = red blood cell; T4: Total thyroxine; TSH: Thyroid-stimulating hormone; WBC = white blood cell.

a. Performing only when urine dipstick analysis is positive.

b. Performing only on 45-60 year-old females who have been amenorrhea for at least 2 years.

c. Screening only.

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.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Followup, and Reporting

10.3.1. Definition of AE

AE Definition

- An AE is any untoward medical occunence 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 abno1mal laborato1y finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

- Any abno1mal laborato1y test results (hematology, clinical chemistiy, 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 abno1mal laborato1y test results that meet any of the conditions below must be recorded as an AE.
  - Is associated with accompanying symptoms.
  - Requires additional diagnostic testing or medical/surgical intervention.
  - Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant dtug treatment, or other therapy.
- Exacerbation of a chronic or inte1mittent 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 stmt of the study.
- Signs, symptoms, or the clinical sequelae of a suspected dtug-dt·ug 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 rep01ted as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-hmming intent. Such overdoses should be repo1ted regm·dless of sequelae.

Events	Meeting the AE Definition
	• Any clinically significant abno1mal laborato1y findings or other abno1mal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the paiticipant'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 paiticipant's condition. • Medical or smgical procedme (eg, endoscopy, appendectomy): the condition that leads to the procedme is the AE. • Situations in which an untoward medical occU1Tence did not occm (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 stait of the study that do not worsen.

10.3.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:

a. Results in death

b. Is **life-threatening**

The te1m "life-threatening" in the definition of "serious" refers to an event in which the paiticipant 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 pa1ticipant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occm dming hospitalization ai·e 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 necessaiy, 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 te1m disability means a substantial disrnption of a person's ability to conduct n01mal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, dianhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent eve1yday life functions but do not constitute a substantial disrnption.

e. Is a congenital anomaly/birth defect

f. Is a 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 laborato1y findings indicating an infection in a paiticipant exposed to a Pfizer product. The te1ms "suspected transmission" and "transmission" ai·e considered synonymous. These cases are considered unexpected and handled as serious expedited cases by phannacovigilance personnel. Such cases ai·e also considered for rep01ting as product defects, if appropriate.

ɡ. **Other situations:**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopai·dize 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 drng dependency or drng abuse.

10.3.3. Recording/Reporting and Followup of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summai·izes the requirements for recording AEs on the CRF and for reporting SAEs on the CT SAE Report Fo1m to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (I) 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,	All AEs/SAEs associated with exposure during pregnancy or breastfeeding **Note:** Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF.	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE).**
Environmental or occupational exposure to the product under study to a non-participant (not involving EDP or EDB)	None. Exposure to a study non-participant is not collected on the CRF.	The exposure (whether or not there is an associated AE or SAE) must be reported.***

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

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

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

- When an AE/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 pruiicipant's medical records to Pfizer Safety in lieu of completion of the CT SAE Repo1i Fonn/AE/SAE CRF page.

- There may be instances when copies of medical records for ce1iain cases are requested by Pfizer Safety. In this case, all pa1ticipant identifiers, with the exception of the pruticipant 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 info1mation. 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 repo1ted during the study and assign it to 1 of the following categories:

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instnnnental ADL. Instrnmental ADL refers to prepru·ing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

- Severe: Severe or medically significant but not immediately life-threatening hospitalization or prolongation of hospitalization indicated; disabling, limiting self case ADL. Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occmTence of each AE/SAE. The investigator will use clinical judgement to dete1mine the relationship.

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

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or product info1mation, 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 or SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occmTed and the investigator has minimal info1mation 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 info1mation and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when dete1mining regulat01y 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 pmposes, as defined by the sponsor. In addition, if the investigator dete1mines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and repo1i such an assessment in the dedicated section of the CT SAE Report Fo1m and in accordance with the SAE rep01iing requirements.

Follow up of AEs and SAEs

- The investigator is obligated to perfo1m or anange 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 laborato1y tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a pa1iicipant dies during pa1iicipation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmo1iem findings, including histopathology.

- New or updated info1mation will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the info1mation.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primaiy mechanism for repo11ing 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 repo11 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 enhy of new data or changes to existing data.
- If a site receives a repo11 of a new SAE from a study paiiicipant or receives updated data on a previously repo1ied SAE after the electi·onic data collection tool has been taken off-line, then the site can report this infonnation on a paper SAE fo1m (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 Repo11 Fo1m is the prefened method to transmit this info1mation to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Fo1m sent by overnight mail or com .er -i se1v1ce.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Repo11 Fo1m pages within the designated repo11ing time frames.

10.4. Appendix 4: Contraception Methods

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(s):

- 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.

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), preferably with low user dependency, 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 study intervention(s). 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

Highly Effective Methods That Have Low User Dependency

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

Intrauterine device (IUD).

2. Intrauterine hormone-releasing system (IUS).

3. Bilateral tubal occlusion.

4. Vasectomized partner.

    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP 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.

Highly Effective Methods That Are User Dependent

5. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

    - Oral;

    - Intravaginal;

    - Transdermal.

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

    - Oral;

    - Injectable.

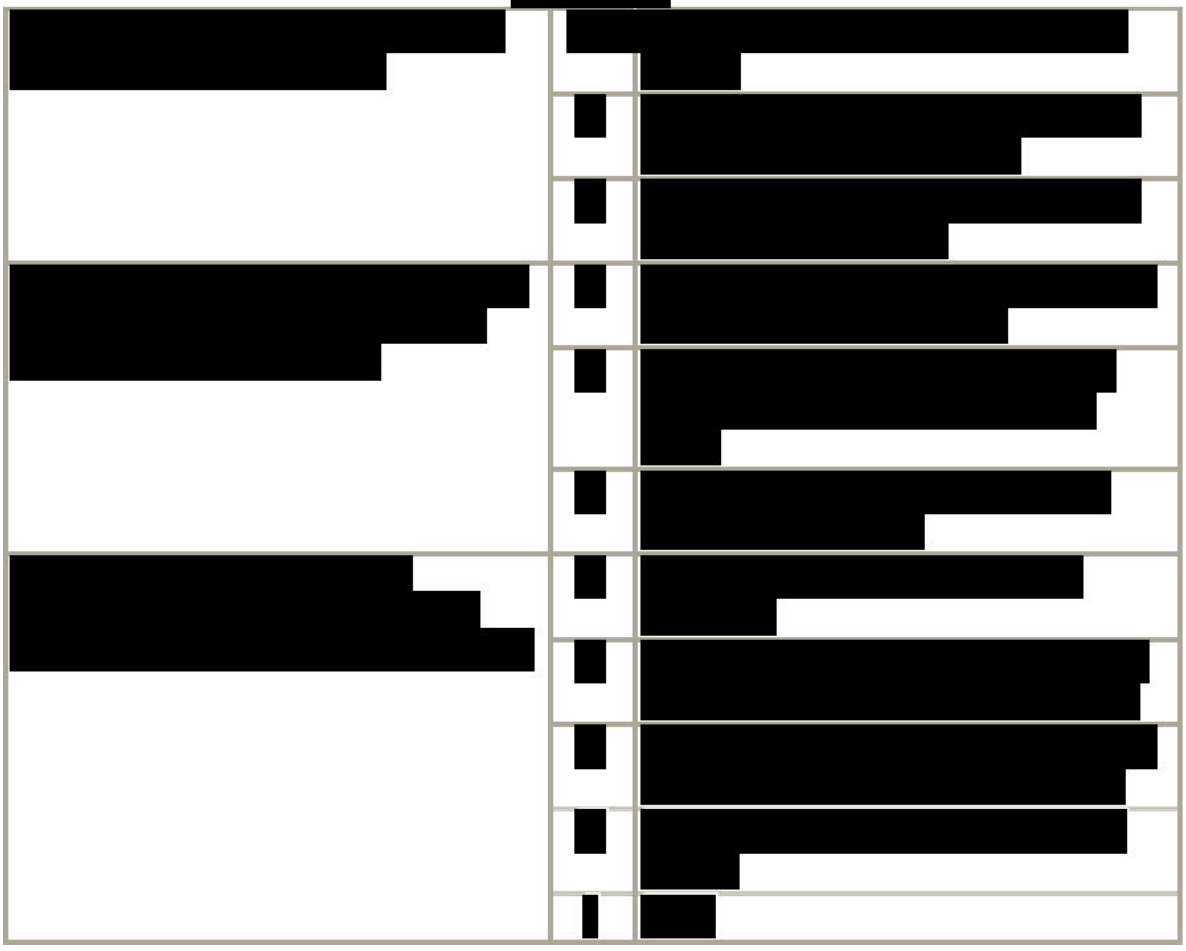
7. Sexual abstinence:

    - 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. CCI [redacted]

[redacted]

[redacted]



10.6. Appendix 6: Liver Safety: Suggested Actions and Followup 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) AV(atrioventricular) 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 asystole3.0 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 >120bpm.

- Sustained supraventricular tachycardia (rate>120 bpm) ("sustained"= sho1i 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/polymo1phic ventricular tachycardia>100 bpm (such as torsades de pointes).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heaii block.

ECG Findings That Qualify as Serious Adverse Events

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyaIThythmias (>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.
- Ventriculai·fibrillation/flutter.
- At the discretion of the investigator, any aiThythmia classified as an adverse expenence.

The enumerated list of major events of potential clinical concern are recommended as "ale1ts" or notifications from the core ECG laboratoty 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. CCI

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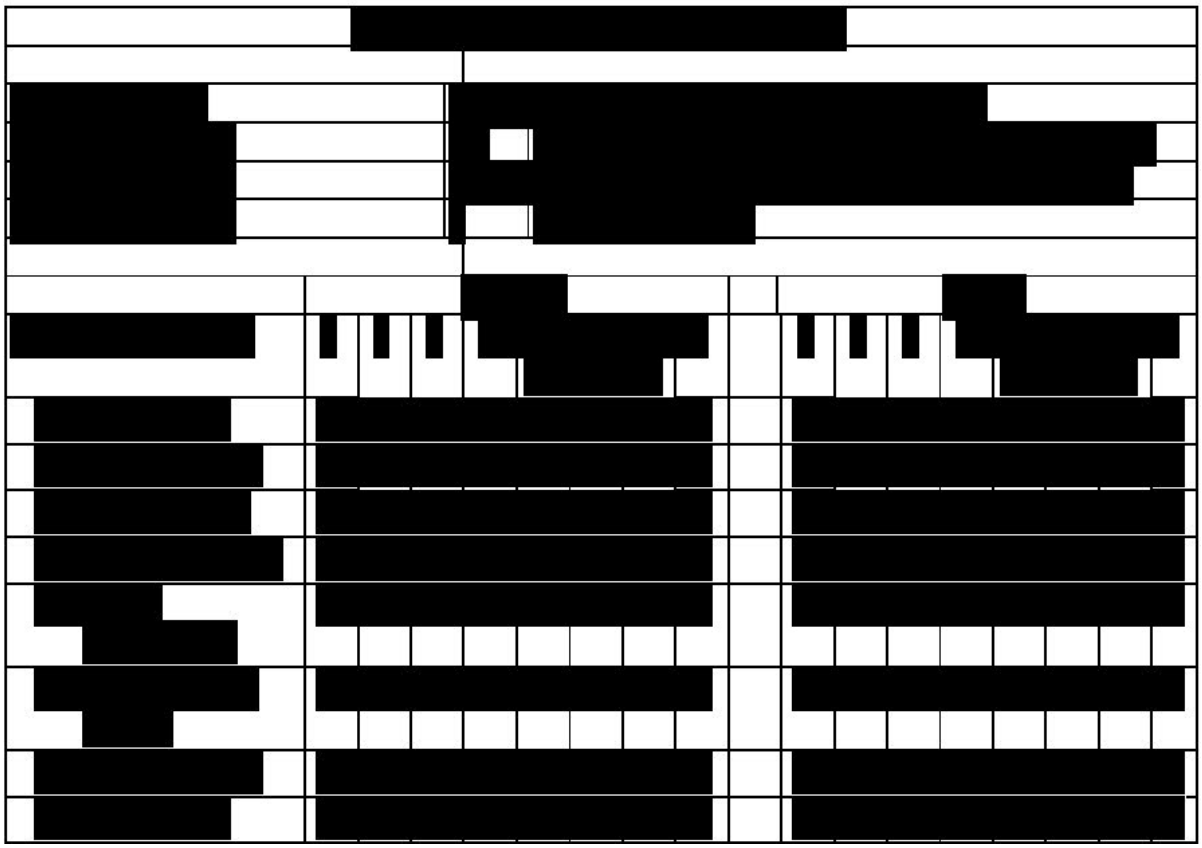

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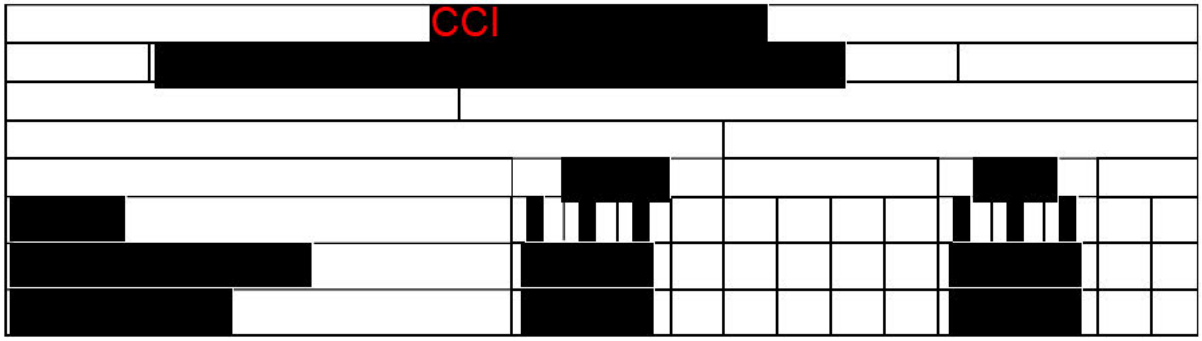
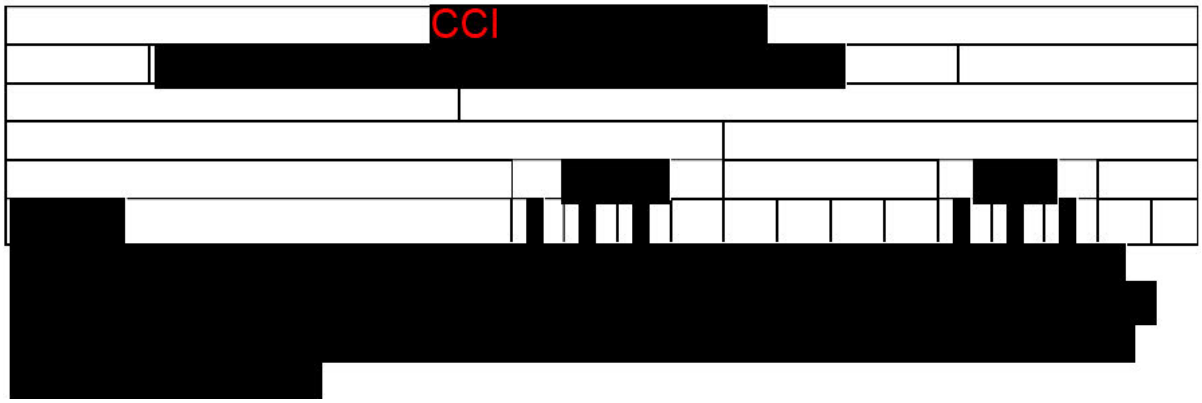


Touch-pressure, pin-prick and vibration sensation are tested on the dorsal surface, at the base of the nail, of the tenninal phalanx of the great toe. Touch-pressure is assessed with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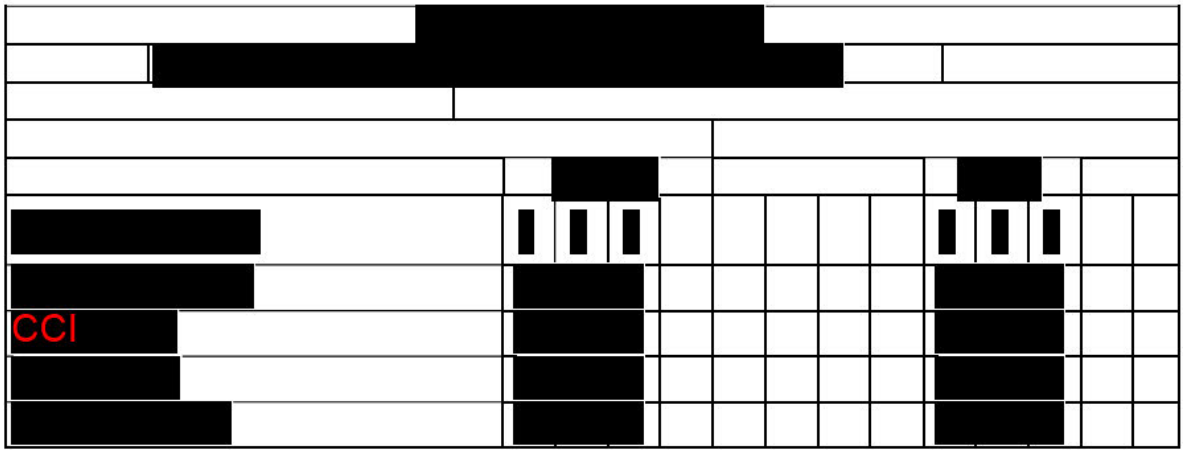
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10.9. Appendix 9: Alternative Measures During Public Emergencies

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 SoA for the nearest missing visit (especially the visit of Week 72 or early study discontinuation), 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.

10.9.1. Eligibility

While SARS-CoV2 testing is not mandated for this study, local clinical practice standards for testing should be followed. A participant 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. Participants with active infections are excluded from study participation as per **Exclusion Criteria 1 (medical conditions).** When the infection resolves, the participant 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.

10.9.2. 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 SoA 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 Appendix 4 and Section 10.9.3.1 of this appendix regarding pregnancy tests.

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

10.9.3. 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 10.9.3.1, 10.9.3.2 and 10.9.3.3 below.

10.9.3.1. 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 3. Protocol Required Safety Laboratory Assessments Permitted at a Local Laboratory

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN/Urea and creatinine Glucose (fasting) Ca++ Na+, K+, Cl- TotalCO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Gamma glutamyl transferase (GGT) Uric acid Albumin Total protein Total Cholesterol Serum pregnancy testing Inorganic Phosphorous Globulin Thyroid-stimulating hormone (TSH) Total thyroxine (T4) Free T4 NT-pro-BNP Troponin I/Troponin T	Protein Nitrites Leukocytes (qualitative) Occult blood Microscopy and culture[a]	Coagulation Panel (PT, PTT, and INR) Retinol-binding protein

Abbreviations: Abs = absolute; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CO_2 = carbon dioxide; Ca = Calcium; Cl = Chlorine; GGT: Gamma glutamyl transferase; Hb = Hemoglobin; INR = international normalized ratio; K = potassium; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; Na = sodium; NT-pro-BNP = N-terminal B-type natriuretic peptide; PT = prothrombin time; PTT = Partial Thromboplastin Time; qual = qualitative; RBC = red blood cell; TSH: Thyroid-stimulating hormone; T4: Total thyroxine; WBC = white blood cell.

a. Performing only when urine dipstick analysis is positive.

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 IU/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.

10.9.3.2. 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.

10.9.3.3. 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.

10.9.4. 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 meglumine may be shipped by courier to study participants if permitted by local regulations and in accordance with storage and transportation requirements for the tafamidis meglumine. Pfizer does not permit the shipment of tafamidis meglumine by mail. The tracking record of shipments and the chain of custody of tafamidis meglumine 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.

10.9.5. Home Health Visits

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

10.9.6. 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.

10.9.7. Efficacy Assessments

Efficacy assessment, including body weight, serum albumin level, Neuropathy Impairment Score-Lower Limb (NIS-LL) 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 participant report outcomes, including Norfolk QOL-DN, SF-36 and EQ-5D-5L, 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, blood sample will not be collected at the alternative facility due to the complexity of sample management.

10.9.8. Independent Oversight Committees

This study will not use an Independent Oversight Committee.

10.10. Appendix 10: Protocol Amendment History

The Protocol Amendment Summa1y of Changes Table for the cmrent amendment is located directly before the TOC. The protocol amendment summaiy of changes tables for past amendment(s) can be found below:

Amendment 2 (20 April 2021)

Section# and Name	Description of Change	Brief Rationale
Protocol Title	• The protocol title was **revised** to *A single arm, multicenter, open-label study to evaluate the efficacy, safety, tolerability, and phannacodynamics of orally administered tafamidis meglumine on in transthyretin amyloid po yneuropathy participants in china.*	For better description of the study characteristic.
Section 1.1 Synopsis Section 2 INTRODUCTION Section 4 STUDY DESIGN	• The study design was **changed** from *This study is designed to determine the effect of tafamidis meglumine on TTR stabilization as well as tafamidis meglumine safety, tolerability and efficacy in ATTR-PN patients in China* to *This study is designed to evaluate the efficacy, safety, tolerability as well as pharmacodynamics of tafamidis meglumine in ATTR-PN participants in China.*	CCI [redacted]
Section 1.1 Synopsis Section 1.3. Schedule of Activities (SoA) Section 4 STUDY DESIGN Section 10.9 Appendix 9: Alternative Measures During Public Emergencies	• The study intervention duration was **changed** from *24 weeks* to *48 weeks.*	CCI [redacted]

Section # and Name	Descri tion of Chan e	Brief Rationale
Section 1.1 Synopsis Section 3 OBJECTIVES, ESTIMANDS, AND ENDPOINTS Section 9.1.1.1 Primruy Estimands	• The prima1y objective **changed** from *To determine the tafamidis meglumine on transthyretin (TTR) stabilization at steady-state in ATTR-PN patients* to *To evaluate the effect of tafamidis meglumine on clinical efficacy in ATTR-PN participants*. • The secondruy objective **changed** from *To evaluate the safety, tolerability and efficacy of tafamidis meglumine in ATTR-PN participants* to *To evaluate the efficacy, safety, tolerability, and pharmacodynamics of tafamidis meglumine in ATTR-PN participants.* • The prima1y endpoint **changed** from *TTR stabilization at Week 8 compared with Baseline, as measured by a validated immunoturbidimetric assay* to *Change from baseline NIS-LL at Week 48 (Month 12).* • *Neuropathy Impairment Score; NIS-LL (lower limb)* was **changed** to *NIS-LL at other visits than Week 48* in the secondruy endpoints. • In seconda1y endpoint, *TTR stabilization at each follow up visit aft.er Week 8* and *TTR concentration at Day 1 (baseline), Week 8, Week 12 and Week 24* was **changed** to *Pharmacodynamic: TTR stabilization and TTR concentration at Day 1*	[redacted] And NIS-LL c' ange from baseline is proposed as the new primruy endpoint.

Section # and Name	Description of Change	Brief Rationale
	(baseline), Week 8, Week 12, Week 24 and Week 48. *Physical examination* **deleted** from the seconda1y Safety endpoints, because physical examination findings collected dming the study will be considered somce data and will not be required to be repo1ted as safety endpoints.	
	• The prima1y estimands **changed** from *Estimated proportion of patients achieving TTR stabilization at Week 8 in ATTR-PN patients, regardless of whether or not patient continues with/adheres to treatment* to *Descriptive statistics of the NIS-LL change fi-orn baseline at Week 48 (Month 12), regardless of whether or not partidpant continues with/adheres to treatment.*	
Section 1.3. Schedule of Activities (SoA)	• Two columns of Week 36 and Week 48 (or Early Study Discontinuation) were **added** to the SoA.	CCI [redacted] And related assessments were also added to evaluate the efficacy, safety, tolerability and phaimacodynamics of tafamidis meglumine.

Section # and Name	Description of Change	Brief Rationale
Section 1.3. Schedule of Activities (SoA)	• The days in the SoA for *week 4, week 8, week 12, week 24* was **updated.**	The calculation was wrong in the former protocol.
Section 1.3. Schedule of Activities (SoA)	• *A column of Post-study follow-up (28 days after last dose)* was **added** to the SoA, the allowable window is +7 days. The only activity required for this visit is Serious and nonserious adverse events monitoring, with note j. Telephone contact can be used to monitor for adverse events.	To meet the adverse event collection requirement in section 8.3.1.
Section 1.3. Schedule of Activities (SoA)	• Note c was **changed** from *At site visit, the time of last dose taken will be checked and recorded together with the actual blood sampling time* to *Collect samples during site visit. At site visit, the time of last dose taken prior to blood collection for TTR stabilization assay and TTR concentration will be checked and recorded. The actual blood sampling time will be recorded for clarity*.	Refer to the chronology of events in Section 8.
Section 1.3. Schedule of Activities (SoA)	• *TSH, total T4, free T4, RBP* was **added** into Laboratory tests to be consistent with **Table 1**. *NT-pro-BNP, Troponin I/Troponin T, coagulation panel* were **listed** as a separate activity as they will not be tested in some visits. Note *d. All Laboratory tests do not need to be repeated if acceptable screening assessment is performed within 30 days prior to Day 1* was	To avoid unnecessary repeating lab tests within a short period of time.

Section # and Name	Description of Change	Brief Rationale
	added for Laboratory tests on Day 1.	
Section 1.3. Schedule of Activities (SoA) Section 4.1 Overall Design Section 10.9.7 Efficacy Assessments	• *NIS* was **updated** as *NIS-LL* in the activity because only lower limbs are assessed. The abbreviations *NIS* was **updated** as *NIS-LL: Neuropathy Impairment Score-Lower Limb* accordingly below the SoA table.	Only lower limbs are assessed.
Section 1.3. Schedule of Activities (SoA)	• Note f was **simplified** *as NIS-LL testing is performed 2 times at least 24 hours apart within a 1-week period by the same neurologist*.	For protocol internal consistency.
Section 1.3. Schedule of Activities (SoA)	• Note h. *All the assessments and procedures at Day 1 (baseline) visit in the SoA should be completed prior to the investigational product administration on Day 1. Only on Day 1, the investigational product will be administered at site during clinic visit* was **added** to *Dispense investigational product on Day 1 to make sure that all the baseline values are obtained before investigation product administration*.	To make sure that all the baseline values are obtained before investigation product administration.
Section 1.3. Schedule of Activities (SoA)	• Note i. *After Week 12* was **changed** to *Between Week 12 to Week 24, Week 24 and 36, and between Week 36 and 48*.	The follow-up is prolonged due to study extension.
Section 4.1 Overall Design	• *The enrollment will be competitive and the enrollment duration is approximately 16 months* was **deleted.**	The limitation of recruitment was removed upon team's decision.

Section # and Name	Description of Change	Brief Rationale
Section 5.4 Screen Failures	• *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 30 days, the individual inclusion/exclusion criteria may need repeating according to the nature of the medical event and clinical judgement of the investigator* was **added** as paragraph 2 in this section.	For better clarification.
Section 6.5.1 Permitted Medicine	• *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**.	For better clarification.
Section 6.5.2 Excluded Medicine, Treatment and Substances	• *Any investigational drug within 30 days before Day 1 (Baseline) through 8 weeks of study participation* was **changed** to *Any investigational intervention within 30 days before Day 1 (Baseline) and during the study participation*.	Because any investigational intervention (drug or non-drug) should be excluded during the whole study participation.
Section 6.5.2 Excluded Medicine, Treatment and Substances	• *Chronic use of non-protocol approved non-steroidal anti-inflammatory drugs (NSAIDs), defined as greater than 3-4 times/month* was **changed** to *Chronic use of non-protocol approved non-steroidal anti-inflammatory drugs (NSAIDs), defined as greater than 4 times/month*.	Because 3-4 times/month is a confusing criterion.

Section # and Name	Description of Change	Brief Rationale
Section 6.5.2 Excluded Medicine, Treatment and Substances	• Topical ophthalmic NSAIDs administered while the *participant*'s nasal punctum is occluded are also permitted was **added.**	To add some flexibility with concomitant therapies.
Section 6.5.2 Excluded Medicine, Treatment and Substances	• *Use of diflunisal, tauroursodeoxycholate, doxycycline, inotersen or patisiran or any other TTR stabilizing agent within 30 days prior to the study entry and/or during study participation is prohibited* was **added.**	because diflunisal, tauroursodeoxycholate, doxycycline, inotersen or patisiran or any other TTR stabilizing agent can affect TTR stability.
Section 7.1 Discontinuation of Study Intervention	• *A participant may be withdrawn from the study for any of the following reasons* was **updated** as *It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention include the following.*	Per the updated protocol template released on 01 March 2021.
Section 7.1 Discontinuation of Study Intervention	• *In rare instances, it may be necessary for a participant to permanently discontinue investigational product. Per the study estimands, if investigational product is permanently discontinued, the participant will remain in the study to be evaluated for adverse events* was **deleted.**	Per the updated protocol template released on 01 March 2021.
Section 7.1 Discontinuation of Study Intervention	• *If study intervention is permanently discontinued, the participant will remain in the study to be evaluated per SoA* was **added.**	Per the updated protocol template released on 01 March 2021.

Section # and Name	Description of Change	Brief Rationale
Section 7.1 Discontinuation of Study Intervention	• *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 updated protocol template released on 01 March 2021.
Section 7.2 Participant Discontinuation/With drawal From the Study	• *The criteria for withdrawal from the study and the data management for these participants* was **changed** per updated template. • A new section title ***Section 7.2.1*** was **added** before ***Withdrawal of consent.***	Per the updated protocol template released on 01 March 2021.
Section 7.3 Lost to Follow-up	• *Discontinuation of specific sites or of the study as a whole is handled as part of Appendix 1* was **deleted.**	Per the updated protocol template released on 01 March 2021.
Section 8. STUDY ASSESSMENTS AND PROCEDURES	• *All the assessments and procedures at baseline visit in the SoA should be completed prior to the investigational product administration on Day 1* was **added**.	To clarify and emphasize this common practice in all clinical trials which is to avoid any effect of the investigational product on baseline assessments.
Section 8. STUDY ASSESSMENTS AND PROCEDURES	• *At the discretion of the investigator, isolated abnormal tests can be repeated for confirmation. However, the entire panel should not be repeated. In the event the repeated test confirms an abnormal value, no further testing is necessary. The*	To provide instructions under the situation when isolated abnormal tests are detected in screening period.

Section # and Name	Description of Change	Brief Rationale
	abnormal test value from the confirmatory test will be entered into the database and the participant will be considered a screen failure. If the repeat test does not confirm the abnormal value (i.e., it is within the normal range), the investigator is required to again repeat the specific laborat01y test. If this further repeat test confirms a value within the normal range, the last repeated normal value is entered into the database. If the further repeat test value is abnormal, this value will be entered into the database and the participant will be considered a screen failure was **added** as paragraph 7 after *"as applicable".*	
Section 8. STUDY ASSESSMENTS AND PROCEDURES	• *The total volume tak,en 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* was **added in** the last pru:agraph.	For more details about the blood volume collected.
Section 8.1 Efficacy Assessment	• *TTR Stabilization and TTR concentration Measurement* was **moved** from **Section 8.1.1** to **Section 8.6.**	CCI [redacted]
Section 8.1.1 Nemopathy	• The section title was **modified** to *Neuropathy Impairment Score-Lower Limb (NIS-LL)* to	Updated endpoint.

Section # and Name	Description of Change	Brief Rationale
Impairment Score (NIS)	be consistent with the updated endpoint.	
Section 8.1.1 Neuropathy Impairment Score (NIS)	• The wording of paragraph 1, 2 and 3 was **revised** accordingly.	Only NIS-LL is to be tested in the study.
Section 8.2.1 Physical Examinations	• *Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.3.1 to 8.3.3* was **added**.	Per the updated protocol template released on 01 March 2021.
Section 8.2.6.2 Biopsy Documentation of Amyloid	• *Or other analysis can be utilized to confirm the deposit of amyloid* was **added** behind 'apple-green' birefringence,	To add some flexibility for the acceptable biopsy analysis methods for the confirmation of amyloid deposition.
Section 8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting	• The whole section was **updated**.	Per the new protocol template with more specific requirements of reporting and collecting AEs.
Section 8.3.1 Time Period and Frequency for Collecting AE and SAE Information	• In paragraph 3, and Pfizer concurs with that assessment was **deleted**.	Per updated template.
Section 8.3.1.1 Reporting SAEs to Pfizer Safety	• The section was **updated**	Per the new protocol template with more specific requirement to

Section # and Name	Description of Change	Brief Rationale
		report SAEs to Pfizer Safety.
Section 8.3.1.2 Recording Nonserious AEs and SAEs on the CRF	• *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.*	Per updated template.
Section 8.3.4 Regulatory Reporting Requirements for SAEs	• *an investigator safety report* was **changed** to *SUSARs*. • *investigator's brochure* was **changed** to *SRSD(s)*.	Per updated template.
Section 8.3.5 Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure	• The whole section was **updated**.	Per the new protocol template with more specific instruction to define EDP, breastfeeding and occupational exposure for investigators.
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	• The whole section was **updated**.	Per the new protocol template with very specific requirement to report and manage an exposure during breastfeeding for investigators.

Section # and Name	Description of Change	Brief Rationale
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.
Section 8.3.6. Cardiovascular and Death Events	• This new section was **added** per updated template.	Per updated template.
Section 8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs	• all the content in the previous section of Hospitalization was **removed** to this section.	The content in section Hospitalization fits the definition of Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs.
Section 8.3.9.1 Lack of Efficacy	• *Lack of efficacy in an approved indication should be reported as an SAE to Pfizer Safety* was **changed** to *The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety only if associated with an SAE*.	Per updated template.
A new section Section 8.3.10. Medical Device Deficiencies was **added** per updated template.		
A new section Section 8.7 Immunogenicity Assessment was **added** per updated template.		
Section 9.2 Sample Size Determination:	• The whole section was **simplified** as *Due to the practical limitation of eligible patients, around 10-15 participants will be enrolled in this study*.	For better clarification.
Section 9.4 Statistical Analyses: Section	• The content in Section 9.4.4 is **simplified** as *Declaring a*	For better clarification as TTR Stabilization is not

Section # and Name	Description of Change	Brief Rationale
TTR Stabilization was **moved** to Section 9.4.4 TTR Stabilization and TTR concentration in Pharmacodynamics	*participant to have been "stabilized" is defined as percent stabilization equal to or greater than 32%. All pharmacodynamic analyses will be performed on the pharmacodynamic population. TTR concentration and percent stabilization will be summarized descriptively, as continuous measures, by visit, regardless of whether or not participant continues with/adhere to treatment. 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, by visit, regardless of whether or not participant continues with/adhere to treatment.*	considered as efficacy endpoints.
Section 9.4.1.1 Neuropathy Impairment Score (NIS)	• The section title was **modified** to *Neuropathy Impairment Score-Lower Limb (NIS-LL)* to be consistent with the secondary endpoint. • *NIS* in this section was **modified** as *NIS-LL*. • The NIS will provide a total body single score of neuropathic deficits and subset scores for cranial nerves (sum of Items 1-5), muscle weakness (sum of Items 6-24), reflexes (sum of Items 25-29), and sensation (sum of Items 30-37).	Only NIS-LL score, not total NIS score, is calculated in this study.

Section # and Name	Description of Change	Brief Rationale
	The total score is the sum of all items was **deleted**.	
Section 10.1.3 Informed Consent Process	• *A participant who is rescreened is not required to sign another ICD if the rescreening does not exceed 30 days from the previous ICD signature date* was **added.**	To add some flexibility for some participants who recover from acute medical conditions.
Section 10.1.8 Study and Site Closure .	• *The study start date is the date on which the clinical study will be open for recruitment of participants. The first act of recruitment is the date of the first participant's first visit and will be the study start date* was **added** as the 1st and 2nd paragraph. • *If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up* was **added** after *Reasons for the early closure of a study site by the sponsor may include but are not limited to:*.	Per the updated protocol template.

Section 10.1.10 Sponsor's Qualified Medical Personnel:
The whole section was **updated** per the protocol template released on 01 March 2021.

Section # and Name	Description of Change	Brief Rationale
Table 1 Protocol-Required Safety Laboratory Assessments Table 2 Protocol-Required Safety Laboratory Assessments permitted at a local laboratory	• *Inorganic Phosphorous, Globulin, Thyroid-stimulating hormone (TSH), Total thyroxine (T4), Free T4, NT-pro-BNP, Troponin I* were **moved** from *Other* to *Chemistry* as they are chemistry parameters. • *Troponin I* was **revised** as *Troponin I/Troponin T,* and *BUN* was revised as *BUN/Urea* for site feasibility reasons. • *Pre-albumin (transthyretin)* was **deleted** from *Other* in this table, because it is presented as TTR concentrations (pharmacodynamics assessment) and is not a safety laboratory assessment.	For better clarification and for site feasibility reasons.

Section 10.3.1 Definition of AE:
The whole section was **updated** per the new protocol template with more specific conditions to record as AEs for investigators.

Section 10.3.2 Definition of SAE:
The whole section was **updated** per the new protocol template with more specific conditions to record as SAEs for investigators.

Section 10.3.3 Recording/Reporting and Follow up of AEs and/or SAEs:
The whole section was **updated** per the new protocol template with more specific requirements to record and manage events as AE/SAEs, more specific instruction of assessment of intensity for each AE/SAE, and more instructions for follow-up AEs and SAEs for investigators.

Section 10.4 Appendix 4: Contraception Methods	• The section title was **changed** from Contraceptive Guidance and Collection of Pregnancy Information to *Contraception Methods.* • All the content under *Collection of Pregnancy*	Per the updated protocol template.

Section # and Name	Description of Change	Brief Rationale
	Information was **deleted** because it was duplicated in section 8.3.5.	
Section 10.8 Appendix 8: Neuropathy Impairment Score	• **(NIS)**: the section title was **changed** to *Appendix 8: Neuropathy Impairment Score-Lower Limb (NIS-LL)*, and the scale was **simplified** to NIS-LL related content only.	Only lower limbs will be assessed in the study now, NIS scale was simplified as NIS-LL scale in this amendment.

Patient(s) or *subject(s)* was **changed** to *participant(s)* throughout the protocol per the latest protocol template.

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

Amendment 1 (20 August 2020)

Section # and Name	Description of Change	Brief Rationale
TABLE OF CONTENTS Schedule of Activities (Section 1.3) Objectives, Estimands, and Endpoints (Section 1.1 Synopsis and Section 3) Overall Design (Section 4.1) Excluded Medicine, Treatment and Substances (Section 6.5.2)	• "*Σ7 NTs NDS*" as measured by nerve conduction studies (NCS), vibration detection threshold (VDT) and heart rate response to deep breathing (HRDB) was **deleted** from secondary endpoint and all related components.	There is no China regulatory agency certified equipment that would allow Investigators to perform quantitative sensory testing (QST), nerve conduction studies (NCS), vibration detection threshold (VDT) and heart rate response to deep breathing assessment) (HRDB).

Section # and Name	Description of Change	Brief Rationale
Study ASSESSMENTS AND PROCEDURES (Section 8) Statistical Considerations (Section 9) Appendix 10: Abbreviations (Section 10.10). REFERENCE (Section 11).		
Protocol Title	• The protocol title was **revised** to *A single arm, multicenter, open-label study to determine the effect of orally administered tafamidis meglumine on transthyretin stabilization, safety, tolerability and efficacy in transthyretin amyloid polyneuropathy patients in china.*	For better description of the study characteristic.
Section 1.1 Synopsis Section 4.1 Overall Design Section 4.2 Scientific Rationale for Study Design Section 9.2 Sample Size Determination	• Number of Participants was **changed** from *Approximately 10* to *Approximately 10-15*.	CCI [redacted]
Section 1.1 Synopsis	• *The enrollment will be competitive and the enrollment duration is approximately*	CCI [redacted]

Section # and Name	Description of Change	Brief Rationale
Section 4.1 Overall Design	*16 months.* CCI [redacted]	
Section 1.1 Synopsis: The sho1i title was **updated** to be in line with the sho1i title on page 1.		
Synopsis (Section 1.1) Introduction (Section 2) Objectives, Estimands, and Endpoints (Section 3) Overall Design (Section 4.1) Scientific Rationale for Study Design (Section 4.2)	• The primaiy objective of the study was **changed** from *To determine transthyretin (TTR) stabilization* to *To detennine the effect of tafamidis meglumine on transthyretin (TTR) stabilization.*	To be consistent with protocol title.
Synopsis (Section 1.1) Objectives, Estimands, Endpoints (Section 3) Safety Analyses (Section 9.4.2)	• *Heart rate* was **changed** to *pulse rate* in secondaiy endpoints.	To be consistent with the rest of protocol.
Section 1.3 Schedule of Activities (SoA)	• *HIV-I and -2 antibodies test* was **changed** to *to HIV antibody.*	For better clai·ification.
Section 1.3 Schedule of Activities (SoA)	• *Karnofsky Performance Status assessment* was **added** to screening assessments.	This was missing in original protocol.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities (SoA)	• *QST for vibration perception in the feet utilizing CASE IV* was **removed** from screening assessments.	Certified CASE IV equipment is not available in China. certified CASE IV equipment is not available in China.
Section 1.3 Schedule of Activities (SoA)	• *QST (CASE IV), HRDB, and NCS assessments* were **removed** from Schedule of Activities (SoA) table.	Certified equipment is not available in China.
Section 1.3 Schedule of Activities (SoA)	• *ECG* was **deleted** at Week 4 and Week 12.	There are no potential or identified risks of acute or subacute ECG changes nor for that matter cardiac risks in the previous clinical data.
Section 1.3 Schedule of Activities (SoA)	• SoA Footnote *b.sampling 3 hours after dosing tafamidis* was **changed** to *b. At site visit, the time of last dose taken will be checked and recorded on the relevant CRF page, together with the actual blood sampling time.*	For better clarification.
Section 2.2.4 Clinical Overview	• **Update** the clinical development programs	According to the latest clinical development plan.
Section 5.2 Exclusion Criteria:	• Text "*Participant has no recordable sensory threshold for vibration perception in both feet, as measured by CASE IV*" was **removed** from exclusion criteria 8.	Due to unavailability of certificated CASE IV equipment in China necessary to perform QST.
Section 5.2 Exclusion Criteria: Prior/Concomitant Therapy	• *Inotersen and patisiran* were **added**.	As they are TTR stabilizing agents.

Section # and Name	Description of Change	Brief Rationale
Section 6.5.2 Excluded Medicine, Treatment and Substances Section 6.1 Study Intervention(s) Administered	• The package used in China was **updated**.	According to the local label from *in bottles of 40 capsules* to *in packs of 30 x 1 soft capsules*.
Section 8 STUDY ASSESSMENTS AND PROCEDURES	• The total blood sampling volume and maximum total volume for individual participants was **updated**.	Re-calculation.
Section 8.1.1 TTR Stabilization and TTR Concentration Measurement	• *At 3 hours after dosing at Week 8, and at Week 12 and 24 (or Early Study Discontinuation)* was **changed** to *and after ECG, blood pressure/pulse rate collection and blood sample collection for clinical laboratory tests during the study visit at Week 8, Week 12 and 24 (or Early Study Discontinuation)*.	The TTR stabilization and TTR concentration will be quite stable at Week 8, so the limit of 3 hours after dosing at Week 8 will not be necessary.
Section 8.2.3 Electrocardiograms	• *QTc* was **changed** to *QTcF* wherever applicable	To make the description more scientific and accurate.
Section 8.6 Pharmacodynamics (PD)	• *PD parameters of TTR stabilization and TTR concentrations* were **changed** from primary endpoint to efficacy endpoint (both primary and secondary endpoint).	For protocol internal consistency.
Section 9.4.1 Efficacy Analysis	• The paragraph of all efficacy analyses was **moved** from	For better clarification.

Section # and Name	Description of Change	Brief Rationale
	Section 9.4.1.1 to Section 9.4.1.	
Section 10.2 Appendix 2: Clinical Laboratory Tests, Table 1	• HIV-1 and -2 antibodies test was **changed** to HIV antibody. • Troponin 1 was **corrected** to Troponin I.	For better clarification.
Section 10.2 Appendix 2: Clinical Laboratory Tests, Table 1	• *PH, glucose, ketones, bilirubin, urobilinogen, specific gravity* were deleted, and *leukocytes (qualitative), microscopy and culture* was **added** in urinalysis.	Some are unnecessary parameters since there is a lab chemistry, and leukocytes, microscopy and culture are essential to detect urinary tract infection.
Section 10.2 Appendix 2: Clinical Laboratory Tests, Table 1	• *Blood (free Hb)* was **changed** to *Occult blood.*	To meet the clinical practice in China.
Section 10.8/10.9/10.11 Appendix 8/9/11:	• All 3 patient report scales were **deleted**.	Due to copyright reasons, and will be provided as separate documents.

A new **Section 10.9 Appendix 9: Alternative Measures During Public Emergencies** was added due to the requirement of new protocol template.

Delete *gelatin* and add *meglumine* in the investigational drug throughout the document wherever applicable to be consistent with the local label.

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

10.11. Abbreviations

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

Abbreviation	Term
Abs	Absolute
ADL	Activities of Daily Living
ADR	Adverse Drug Reaction
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATTR	transthyretin amyloid
ATTR-CM	transthyretin amyloid cardiomyopathy
ATTR-PN	transthyretin amyloid polyneuropathy
AUC	area under the curve
AV	atrioventricular
BA	bioavailability
BE	bioequivalence
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
Ca	calcium
CCI	[redacted]
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
Cl	chloride
C_{max}	maximum observed concentration
CO_2	carbon dioxide (bicarbonate)
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease-2019
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	clinical study report
CT	clinical trial
CTMS	clinical trial management system
CV	cardiovascular
DCT	data collection tool
DILI	drug-induced liver injury
DMC	data monitoring committee
DRE	disease-related event
DU	dispensable unit

Abbreviation	Term
E/A	E peak/A peak
EC	ethics committee
ECC	Emergency Contact Card
ECG	electrocardiogram
ECHO	Echocardiography
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 trial
EQ-5D-5L	EuroQoL 5 Dimensions 5 Levels
EQ VAS	EuroQoL visual analogue scale
EU	European Union
EudraCT	European Clinical Trials Database
FSH	follicle-stimulating hormone
FOI	fraction of initial tetramer concentration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GH	general health
HbA_{1c}	hemoglobin A_{1c}
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCV	Hepatitis C virus
HCVAb	hepatitis C antibody
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 application
INR	international normalized ratio
IP manual	investigational product manual
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IWR	interactive Web-based response

Abbreviation	Term
K	potassium
K2 EDTA	dipotassium ethylenediaminetetraacetic acid
LBBB	left bundle branch block
LFT	liver function test
mBMI	modified body mass index
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MSC	Mental Component Summary
MCV	mean corpuscular volume
MH	mental health
N/A	not applicable
Na	sodium
NSAID	non-steroidal anti-inflammatory drug
NAb	neutralizing antibodies
NIMP	noninvestigational medicinal product
NIS	Neuropathy Impairment Score
NIS-LL	Neuropathy Impairment Score-lower limb
NMPA	National Medical Products Administration
Norfolk QOL-DN	Norfolk Quality of Life - Diabetic Neuropathy
NT-pro-BNP	N terminal pro B-type natriuretic peptide
PCD	primary completion date
PCS	Physical Component Summary
PD	pharmacodynamic(s)
PE	Physical examination
PF	physical function
PI	principal investigator
PK	pharmacokinetic(s)
PT	prothrombin time
PTT	Partial Thromboplastin Time
PVC	premature ventricular complexe
QD	Once daily
QOL	Quality of Life
OTC	Over-the-counter
QTc	corrected QT
QTcB	corrected QT (Bazetts method)
QTcF	corrected QT (Fridericia method)
qual	qualitative
RBC	red blood cell
RBP	Retinol-binding protein
RE	role-emotional
RP	role-physical
SARS-CoV2	Severe Acute Respiratory Syndrome-Coronavirus 2002

Abbreviation	Term
SAE	serious adverse event
SAP	statistical analysis plan
SF	social function
SF-36	36-Item Short Form Survey
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SToD	study team on demand
SUSAR	suspected unexpected serious adverse reaction
T4	Thyroxine
TESPO	Tafamidis Enhanced Surveillance of Pregnancy Outcomes
THAOS	Transthyretin-Associated Amyloidosis Outcomes Surve
Tmax	time of maximum observed concentration
TBili	total bilirubin
TQOL	Total Quality of Life
TSH	Thyroid-stimulating hormone
TTR	transthyretin
TTR-FAP	Transthyretin Familial Amyloid Polyneuropathy
TOC	table of contents
ULN	upper limit of normal
US	United States
Val30Met	substitution of methionine for valine at position 30
VT	vitality
WBC	white blood cell
WOCBP	woman of childbearing potential

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