# NON-INTERVENTIONAL (NI) STUDY PROTOCOL

## PASS Information

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| **Title** | Transthyretin Amyloidosis Outcomes Survey (THAOS): A Global, Multi-Center, Longitudinal, Observational Survey of Patients With Documented Transthyretin Gene Mutations or Wild-Type Transthyretin Amyloidosis |
| **Protocol number** | B3461001 |
| **Protocol version identifier** | Protocol Amendment 5, 13 July 2020 |
| **Date of last version of protocol** | 07 July 2015 |
| **Active substance** | N07XX08 tafamidis |
| **Medicinal product** | tafamidis |
| **Product reference** | EU/1/11/717/001-004 |
| **Procedure number** | EMEA/H/C/002294/XX |
| **Marketing Authorization Holder (MAH)** | Pfizer Europe MA EEIG |
| **Joint Post-Authorization Safety Study (PASS)** | No |
| **Research question and objectives** | The Transthyretin Amyloidosis Outcomes Survey (THAOS) is a longitudinal, observational survey open to all patients with transthyretin- amyloidosis and participants with transthyretin (TTR) gene mutations without a diagnosis of transthyretin amyloidosis (ATTR amyloidosis). To date, limited data are available on the natural history of the hereditary and wild-type forms of the disease, including the regional differences in disease expression by TTR variants and non- |

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| | mutated TTR, and the genotypic-phenotypic relationship in ATTR amyloidosis.<br><br>The principal aims of the outcome survey are to better understand and characterize the natural history of the disease by studying a large and heterogeneous patient population. |
| **Country(ies /Regions of study** | Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Cyprus, Denmark, France, Germany, Greece, Israel, Italy, Japan, Korea, Luxembourg, Macedonia, Malaysia, Mexico, Netherlands, People's Republic of China, Portugal, Republic of China, Taiwan, Romania, Spain, Sweden, Switzerland, Turkey, United States |
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**Marketing Authorisation Holder(s)**

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## 1. TABLE OF CONTENTS

## 2. LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| AE | Adverse event |
| ATTR | Amyloid fibril protein derived from misfolded TTR |
| ATTR amyloidosis | Disease resulting from deposition of ATTR |
| ATTR-CM | Transthyretin amyloid cardiomyopathy (formerly TTR-CM, or Senile Systemic Amyloidosis) |
| ATTRm | ATTR due to a hereditary mutation |
| ATTR-PN | Transthyretin amyloid polyneuropathy (formerly TTR-FAP) |
| ATTRwt | ATTR due to wild type mutation |
| CHMP | Committee for Medicinal Products for Human Use |
| CIOMS | Council for International Organizations of Medical Sciences |
| CRF | Case Report Form |
| CSR | Clinical study agreement |
| DCTs | Data collection tools |
| EDP | Exposure During Pregnancy |
| EMA | European Medicines Agency |
| EMEA | European Medicines Evaluation Agency |
| ENCePP | European Network of Centres for Pharmacoepidemiology and Pharmacovigilance |
| CCI | [redacted] |
| EU | European Union |
| EU-CHMP | European Union Committee for Medicinal Products for Human Use |
| FAC | Familial Amyloid Cardiomyopathy |
| FAP | Familial Amyloid Polyneuropathy |
| FDA | Food and Drug Administration |
| GFR | Glomerular Filtration Rate |
| GPP | Good Pharmacoepidemiology Practices |
| ICH | International Conference on Harmonization |

| Abbreviation | Definition |
|---|---|
| IRB/IEC | Institutional Review Board /Independent Ethics Committee |
| ISPE | International Society for Pharmacoepidemiology |
| ISPOR | International Society for Pharmacoeconomics and Outcomes Research |
| CCI | [redacted] |
| NI | Non-interventional |
| NIS AEM | Non-Interventional Study Adverse Event Monitoring |
| CCI [redacted] | [redacted] |
| [redacted] | [redacted] |
| PhRMA | Pharmaceutical Research and Manufacturers Association |
| PASS | Post-Authorization Safety Study |
| PI | Principal Investigator |
| QoL | Quality of life |
| RMP | European Medicines Agency Risk Management Plan |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SSA | Senile Systemic Amyloidosis |
| TESPO | Tafamidis Enhanced Surveillance for Pregnancy Outcomes |
| THAOS | Transthyretin Amyloidosis Outcomes Survey |
| TTR | Transthyretin |
| TTR-CM | Transthyretin cardiomyopathy (now ATTR-CM) |
| TTR-FAP | Transthyretin familial amyloid polyneuropathy (now ATTR-PN) |
| US | United States |
| UTI | Urinary Tract Infection |
| Val30Met | Substitution of methionine for valine at position 30 |

## 3. RESPONSIBLE PARTIES

### Principal Investigator(s) of the Protocol

The contact details for the Principal Investigators in the Transthyretin Amyloidosis Outcomes Survey (THAOS) are available upon request.

### Country Coordinating Investigators

The contact details for the Principal Investigators who serve as the Country Coordinating Investigators in the Transthyretin Amyloidosis Outcomes Survey (THAOS) are available upon request.

## 4. ABSTRACT

**Transthyretin Amyloidosis Outcomes Survey (THAOS): A Global, Multi-Center, Longitudinal, Observational Survey of Patients With Documented Transthyretin Gene Mutations or Wild-Type Transthyretin Amyloidosis (Amendment 5; 13 July 2020, PPD )**

**RATIONALE AND BACKGROUND:** Transthyretin (TTR) amyloidosis is a rare disease caused by dissociation of the transthyretin tetramer into monomers, which misfold, ultimately forming amyloid deposits in various organs. This structural instability of the TTR tetramer can occur due to genetic mutations of the gene encoding the TTR protein or can be associated with aging. There are over 120 known mutations of TTR gene, which result in variable phenotypic expressions of amyloidosis that commonly affect the peripheral nerves, heart, kidney or eye.

The Transthyretin Amyloidosis Outcomes Survey (THAOS) is a longitudinal, observational survey open to all patients with TTR gene mutations without a diagnosis of ATTR amyloidosis and to patients diagnosed with ATTR amyloidosis (inclusive of ATTR-PN and ATTR-CM). To date, limited data are available on the natural history of the hereditary (ATTRm) and wild-type (ATTRwt) forms of the disease, including the regional differences in disease expression by TTR variants and non-mutated TTR, and the genotypic-phenotypic relationship in ATTR amyloidosis.

The principal aims of the outcome survey are to better understand and characterize the natural history of the disease by studying a large and heterogeneous patient population. Survey data may be used to develop new treatment guidelines and recommendations, and to inform and educate clinicians about the management of this disease.

The survey can also generate descriptive safety summaries using adverse and serious adverse event (AE/SAE) data in tafamidis-treated participants.

**RESEARCH QUESTION AND OBJECTIVES:** The objectives of THAOS are to describe the population of patients affected with ATTR amyloidosis and to enhance the understanding of the disease natural history, including the variability and progression of the hereditary and acquired forms of disease.

**STUDY DESIGN**: THAOS is a non-interventional, global, multi-center, longitudinal observational survey open to all patients with ATTR amyloidosis, including both inherited and wild-type forms of disease, and participants with TTR gene mutations without disease diagnosis. There is no set number of patients who will be enrolled. The study has been open since 2007 and will continue until Pfizer declares the study complete (currently estimated to be the year 2023) or as long as patients are able to participate, or until they withdraw consent.

THAOS does not involve the administration of an investigational agent or other intervention. Patients will continue to receive their current medications and all other standard care for their disease. It is recommended that patient assessments be conducted at least annually and be recorded in the THAOS electronic data record close to the time they are performed.

Treatment with tafamidis or with other disease modifying therapies will be according to the product label with commercially available product or according to protocol-specified requirements if a participant is enrolled in a tafamidis interventional study.

In addition to routine procedures for standard of care, patients will be asked to complete patient outcome questionnaires at least annually; these are optional and do not affect a patient's eligibility to participate in the survey.

The survey will be conducted at sites worldwide.

**POPULATION:** The study population includes patients with confirmed hereditary or wild-type ATTR amyloidosis and those with TTR gene mutation without a diagnosis of ATTR amyloidosis.

**VARIABLES:** A series of assessments will be used to assess disease progression and the effects of tafamidis treatment including patient demographics, TTR genetic test results, family disease history, medical history, annual medical assessment, general examination, concomitant medications, hospitalizations, transplant history and complications, AE/SAE reporting for tafamidis-treated subjects, events of interest, clinical laboratory data, urinalysis, cardiovascular assessments, neurologic assessments, eye examination, body composition, CCI and patient death.

**DATA SOURCES:** A computer-based application will be used for entering data into the THAOS electronic data record, allowing sites to enter data remotely through locally secured connections. The THAOS electronic data record allows for data to be recorded from an eligibility/baseline visit, at return visits, and in the form of status updates if the patient has not visited the site. In addition, THAOS physicians have the option of recording pre-baseline retrospective patient data. Final data entry (the entry of a status update indicating that the patient has been discontinued) will occur when the survey is completed, if the patient dies, or elects to discontinue the survey.

**STUDY SIZE:** There is no pre-determined number of enrolled patients or participating sites in THAOS.

**DATA ANALYSIS:** Analysis of clinical outcomes will be conducted on all enrolled patients with available data. Outcomes will be examined for the entire patient group, as well as through stratification of important variables that may affect outcomes (for example, but not limited to, TTR data, age, race, gender, country of origin). Outcomes will include results of the key clinical, functional and Patient Reported Outcome assessments used to define progression of disease.

**MILESTONES:** Safety data required as part of the European Medicines Agency Risk Management Plan (RMP) for tafamidis will be analyzed annually for submission to the relevant regulatory authorities.

# 5. AMENDMENTS AND UPDATES

| Amendment Number | Date | Substantial or Administrative Amendment | Protocol Section(s) Changed | Summary of Amendment(s) | Reason |
|---|---|---|---|---|---|
| 1 | 31-Jul-2007 | Substantial | All | Update disease terms and abbreviation nomenclature. New term hereditary transthyretin amyloidoses ATTR. ATTR-PN, ATTR-CM. | Update disease terms and abbreviation nomenclature. New term hereditary transthyretin amyloidoses ATTR. ATTR-PN, ATTR-CM. |
| 2 | 20-Jan-2010 | Substantial | All | Clarify that a patient may participate in THAOS if enrolled in an open-label or double-blind clinical trial. | Clarify that a patient may participate in THAOS if enrolled in an open-label or double-blind clinical trial. |
| 3 | 30-Sep-2011 | Substantial | All | Addition of Pfizer safety language for adverse event and serious adverse event collection. Addition of safety data collection. Change of sponsor to Pfizer INC. | Addition of Pfizer safety language for adverse event and serious adverse event collection. Addition of safety data collection. Change of sponsor to Pfizer INC. |
| 4 | 07–Jul-2015 | Substantial | All | Significant protocol reformatting according to the requirements for non-interventional post-authorization safety study (PASS) protocols and alignment with appropriate guidance documents. | The proposed protocol has been reformatted according to the requirements for non-interventional post-authorization safety study (PASS) protocols as specified in the European Medicine Agency's (EMA) Guideline on Good Pharmacovigilance Practices: Module VIII – Post-Authorisation Safety Studies (PASS) and Guidance for the Format and Content of the Protocol of Non-Interventional Post-Authorisation Safety Studies. This has resulted in the addition of several sections including PASS information, MAH information, Responsible Parties, Abstract, and Milestones. Changes were made to the Research Methods section to adhere to this format. |
| | | | Section 6.0 Rationale and Background | Section 6.0 Rationale and Background updated to include information for marketing approval of tafamidis for treatment of ATTR in adult | Section updated to include information for marketing approval of tafamidis for treatment of ATTR in adult patients with Stage 1 symptomatic polyneuropathy to delay |

| Amendment Number | Date | Substantial or Administrative Amendment | Protocol Section(s) Changed | Summary of Amendment(s) | Reason |
|---|---|---|---|---|---|
| | | | | patients with Stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment. | peripheral neurologic impairment. |
| | | | Section 8.1 Study Design; 8.4 Data Sources | Language revised to include the ability to record data in the form of status updates for those subjects that have not visited the site. | Language revised to include the ability to record data in the form of status updates for those subjects that have not visited the site. |
| | | | Section 8.2.1 Inclusion Criteria | Inclusion Criteria 3 modified to allow identification of cardiac involvement by echocardiogram. | Inclusion Criteria 3 modified to allow identification of cardiac involvement by echocardiogram.<br><br>Inclusion Criteria #3: Confirmed genotyped TTR mutation with or without a diagnosis of ATTR, or wild-type TTR amyloidosis. Confirmation of wild-type TTR amyloidosis will be determined by genotyped confirmation that patient does not possess a known mutation in TTR gene (ie, is a carrier of wild-type allele only) via genetic testing and one of the following set of criteria: Evidence of cardiac involvement by echocardiogram as defined by mean left ventricle wall thickness of >12 mm, and presence of amyloid in cardiac biopsy tissue confirmed as TTR amyloid by mass spectrometry or; or evidence of cardiac involvement by echocardiogram as defined by mean left ventricle wall thickness of >12 mm, and presence of amyloid in non-cardiac tissue confirmed as TTR amyloid by mass spectrometry or immunohistochemistry or evidence of cardiac involvement by echocardiogram as defined by mean left ventricle wall thickness of >12 mm, no |

| Amendment Number | Date | Substantial or Administrative Amendment | Protocol Section(s) Changed | Summary of Amendment(s) | Reason |
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| | | | | | evidence of primary (light chain) amyloidosis, and presence of amyloid in cardiac tissue indirectly confirmed by scintigraphy with a 'bone seeking tracer' eg, 99mTC-DPD [99Mtc-3,3-diphosphono-1,2-propano-dicarboxylic acid], 99mTC-PYP [Pyrophosphate], and 99mTC-HMDP [hydroxymethylene diphosphonate] with Perugini grade ≥2. |
| | | | Section 8.10.1.3 Safety and efficacy in patients with TTR FAP mutations other than V30M | Section 8.10.1.3 Safety and efficacy in patients with TTR FAP mutations other than V30M added. | Section 8.10.1.3 Safety and efficacy in patients with TTR FAP mutations other than V30M added. |
| | | | Section 9.1.1 Participation in Investigational Clinical Trials | Section 9.1.1 Participation in Investigational Clinical Trials language revised to specify that there will be no reconciliation between databases and to allow for data entry for clinical trial data that was collected during the clinical trial study. | Section 9.1.1 Participation in Investigational Clinical Trials language revised to specify that there will be no reconciliation between databases and to allow for data entry for clinical trial data that was collected during the clinical trial study. Revision: Data collected during the course of the clinical trial may be entered retrospectively at the end of the trial if the THAOS principal investigator obtains and documents approval from the study sponsor who conducted the clinical trial. Retrospective data entry cannot occur until the study has been unblinded, which will permit identification of the treatment received during the trial. No reconciliation between databases will occur. For interventional clinical trials that include open-label tafamidis or other open-label investigational products, patients may |

| Amendment Number | Date | Substantial or Administrative Amendment | Protocol Section(s) Changed | Summary of Amendment(s) | Reason |
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| | | | | | continue in THAOS, with the approval of the Sponsor, but AE data collection will be addressed through the interventional clinical trial sponsor. The THAOS principal investigator is responsible for obtaining and documenting approval from the study sponsor for investigational agents other than tafamidis. |
| | | | Section 10 Management and Reporting of Adverse Events/Adverse Reactions for Tafamidis-Treated Subjects | Language regarding reporting of overdose, misuse, extravasation and occupational exposure within 24 hours was added. | Language regarding reporting of overdose, misuse, extravasation and occupational exposure within 24 hours was added to align with current safety reporting practices. This was previously included in Administrative Update dated 06June2014. |
| | | | Section 10.7 Single Reference Safety Document | Single Reference Safety Document identified. | Single Reference Safety Document identified. Added, "The Product Label should continue to be used by the investigator for prescribing purposes and guidance." This was previously included in Administrative Update dated 12December2013. |
| 5 | 17 January 2020 and including updates to reflect EMA requests 13July2020 | Substantial | Throughout document | The Table of Contents section has now been captured with a page number in the Table of Contents, thus causing each section to be numbered 1 digit higher in protocol amendment 5 when compared to protocol amendment 4. | To conform to the new Pfizer Non-Interventional Study protocol template. |

| Amendment Number | Date | Substantial or Administrative Amendment | Protocol Section(s) Changed | Summary of Amendment(s) | Reason |
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| | | | Throughout document | Nomenclature updated:<br>• from transthyretin-associated amyloidosis to just transthyretin amyloidosis.<br>• from Transthyretin (TTR) Mutations or Wild-Type TTR Amyloidosis to Transthyretin (TTR) Gene Mutations or Wild-Type ATTR Amyloidosis.<br>• from amyloidoses to amyloidosis.<br>• from familial amyloid polyneuropathy (TTR-FAP) to transthyretin amyloid polyneuropathy (ATTR-PN).<br>• from familial amyloid cardiomyopathy (FAC) to transthyretin amyloid cardiomyopathy (ATTR-CM). | As the understanding of ATTR amyloidosis advances, naming conventions are evolving to become more accurate in their description of the disease. |
| | | | Section formerly 6.1/new 7.1 Disease Background | More information on ATTR-CM (cardiomyopathy) was added | To provide further information about clinical features of the pathology. |
| | | | Section formerly 8.2.1/new 9.2.1 Inclusion Criteria | Evidence of cardiac involvement by echocardiogram as defined by mean left ventricle wall thickness of >12 mm was removed from the Inclusion Criteria for wild type patients with presence of TTR amyloid in cardiac tissue confirmed by a cardiac biopsy or scintigraphy. | Positive endomyocardial biopsy or bone scintigraphy with Perugini grade ≥2 are sufficient for identification of cardiac ATTR involvement. |

| Amendment Number | Date | Substantial or Administrative Amendment | Protocol Section(s) Changed | Summary of Amendment(s) | Reason |
|---|---|---|---|---|---|
| | | | Section 9.2 | A footnote was added to Table 1:<br>The following important identified risks (Urinary tract infections, Diarrhea, Upper abdominal pain and Vaginal infections); important potential risks (Hypersensitivity reactions); and missing information (Safety and efficacy in elderly patients and Longer-term safety) have been removed from the list of ongoing safety concerns from the tafamidis EU RMP Update (v 9.3), approved on 17 February 2020. | To clarify the information in Table 1 was not aligned with the tafamidus EU RMP Update (v 9.3), approved on 17 February 2020. |
| | | | Section formerly 8.6/new 9.6 Data Management | The text has been updated with the latest Pfizer protocol template language. | To conform to the new Pfizer Non-Interventional Study protocol template. |
| | | | Section formerly 8.7/new 9.7. Data Analysis | The text has been updated with the latest Pfizer protocol template language. | To conform to the new Pfizer Non-Interventional Study protocol template. |
| | | | Section formerly 8.8.1/new 10 Data protection and patient identification. | Moved to Section 10. | To conform to the new Pfizer Non-Interventional Study protocol template. |
| | | | Section formerly 9/new 10 Protection of Human Subjects. | Patient Information and Consent split into 2 sub-sections. The text has been updated with the latest Pfizer protocol template language. | To conform to the new Pfizer Non-Interventional Study protocol template. |
| | | | Section formerly 8.10/ new 9.10 Other Aspects. | Sub-category "Important Missing Data" removed and "Not Applicable" added. | This was duplicative of the text captured in Table 1. |
| | | | Section formerly 10/new 11 Management and Reporting of Adverse events. | Removed requirement to report Pregnancy of Partner. | As tafamidis has been shown not to be present in seminal fluid and therefore male contraception is not required in the approved Product Information, collection of data regarding the pregnant partner of the |

| Amendment Number | Date | Substantial or Administrative Amendment | Protocol Section(s) Changed | Summary of Amendment(s) | Reason |
|---|---|---|---|---|---|
| | | | | | male recipient of tafamidis is not needed. |
| | | | Annex | CCI [redacted] | [redacted] |

# 6. MILESTONES

| Milestone | Planned date |
|---|---|
| Start of data collection (First Subject First Visit: FSFV) | 16 December 2007 |
| End of data collection (Last Subject Last Visit: LSLV) | 16 June 2023 |
| Study progress report | Study progress reports are submitted to the EMA annually |
| Final study report | 16 May 2024 |

# 7. RATIONALE AND BACKGROUND

## 7.1. Disease Background

Transthyretin (TTR) a 127-amino acid, tetrameric protein, primarily synthesized in the liver, is a secreted protein present in the blood and cerebrospinal fluid and is a carrier of thyroxine and retinol-binding protein-retinol (vitamin A) complex. Transthyretin amyloidosis (ATTR amyloidosis) is a rare disease caused by destabilization and dissociation of the native TTR tetramer into monomers, which can result in misfolding and the formation of amyloid fibrils in various organs in amounts sufficient to impair normal functioning.[1-5]

The 2 major phenotypes which form the spectrum of ATTR amyloidosis are transthyretin amyloid polyneuropathy (ATTR-PN), formerly referred to as transthyretin familial amyloid polyneuropathy (TTR-FAP), which primarily affects the peripheral and autonomic nerves, and transthyretin amyloid cardiomyopathy (ATTR-CM) which primarily affects the myocardium. These clinical manifestations may occur in isolation or together. Both result in progressively impaired function, and ultimately in death.

There are over 130 known mutations of TTR gene,[4] which result in variable phenotypic expressions of amyloidosis that commonly affect the peripheral nerves, heart, kidney or eye.[6,7]

### ATTR-PN

The hereditary forms of ATTR amyloidosis are autosomal dominantly inherited diseases[8,9] with a variable penetrance that can affect multiple generations in a family and have a substantial impact on patients and their families. Val30Met (substitution of methionine for valine at position 30) is the most common mutation associated with ATTR-PN, with symptom onset usually in the third to fourth decade of life, depending on the mutation carried and the patient's ethnic background.[6-11]

The main feature of ATTR-PN is progressive sensorimotor and autonomic neuropathy. Sensory neuropathy typically starts in the lower extremities followed by motor neuropathy within a few years.[8,10,11] Autonomic neuropathy quite often accompanies the sensory and motor deficits.[12] ATTR-PN is more frequently observed in certain areas of Portugal, Sweden, and Japan but has been identified throughout the world.[11] Although penetrance varies greatly among geographic and ethnic foci, the outcome of the disease is invariably progressive and fatal. The lifespan for patients is severely shortened, with death occurring within a mean of 10-15 years from the first symptoms.[14,1]

Disease-modifying therapies for ATTR-PN include TTR stabilizer tafamidis,[30] orthotopic liver transplantation,[13-15] RNA interference (RNAi)-based drugs, and transthyretin-directed antisense oligonucleotide drugs. Tafamidis meglumine was approved in the European Union (EU) on 16 November 2011 for the treatment of ATTR in adult patients with Stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment. Currently, it is approved for ATTR-PN in over 40 countries worldwide. Subsequently, Tegsedi (inotersen) and Onpattro (patisiran) for the treatment of hereditary ATTR amyloidosis in patients with polyneuropathy (ATTR-PN) have also been approved in the EU and US.[16-18]

Tafamidis is a novel specific stabilizer of both tetrameric wild-type (w-t) TTR and of amyloidogenic variants of TTR (ATTR). By binding to the native tetrameric form of TTR, tafamidis inhibits tetramer dissociation, the rate limiting step in the formation of TTR amyloid. By inhibiting TTR amyloid formation, this novel class of TTR stabilizer drug has the potential to disrupt the progression of ATTR. The specificity of the binding to TTR also limits tafamidis to the treatment of ATTR amyloidosis only, with no activity anticipated for other types of amyloidosis. Tafamidis slows the progression of disease and therefore represents a disease modifying therapy.

**ATTR-CM**

ATTR-CM occurs when the amyloid fibrils infiltrate the myocardium, leading to diastolic dysfunction progressing to, heart failure, restrictive cardiomyopathy, and death.[19] ATTR-CM, also known as familial amyloid cardiomyopathy (FAC), is a late-onset disease with symptoms typically occurring in patients over 60 years old.[20] This disease can be inherited as an autosomal dominant trait caused by mutation in the TTR gene (commonly the Val122Ile mutation which occurs with high frequency [prevalence of 3.9%][22] in African-Americans); however, a mutation in TTR gene is not a pre-requisite for developing ATTR-CM. In the elderly, wild-type (normal) TTR may become structurally unstable resulting in deposition of amyloid fibrils primarily in heart tissue and leading to restrictive cardiomyopathy and heart failure.[21]

Wild-type ATTR amyloidosis (previously known as senile systemic amyloidosis (SSA) or senile cardiac amyloidosis,[23-27] is diagnosed based on positive bone scintigraphy[21,29] (Perugini grade ≥2)[30] or confirmed ATTR amyloid by tissue biopsy and immunohistochemical staining, and characteristic echocardiographic abnormalities[21,29] in the absence of a TTR gene mutation and a plasma cell dyscrasia. The clinical presentation of

wild-type ATTR amyloidosis is similar to variant ATTR-CM, with the disease primarily affecting elderly males.[20]

Combined heart and liver transplantation is a treatment option for ATTR-CM, however is limited by organ availability and significant patient co-morbidity.

Tafamidis is currently the only approved treatment for ATTR-CM with approvals in a growing number of countries worldwide including but not limited to: Japan (March 2019) for tafamidis meglumine 80 mg daily in patients with wild-type and variant forms of ATTR-CM; the US (May 2019) for tafamidis meglumine 80 mg daily and tafamidis 61mg daily for the treatment of the cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization; and the EU (February 2020) as a line extension to tafamidis 61 mg daily for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy.

This non-interventional study (disease registry), designated as a post-authorization safety study (PASS) is open to all patients with transthyretin (TTR) gene mutations without a diagnosis of ATTR amyloidosis and to patients diagnosed with ATTR amyloidosis (inclusive of ATTR-PN and ATTR-CM) in agreement with the European Medicine Agency (EMA) until 16 June 2023.

### 7.2. Rationale for the Survey

The Transthyretin Amyloidosis Outcomes Survey (THAOS) is a longitudinal, observational survey open to all patients with TTR gene mutations without a diagnosis of ATTR amyloidosis and to patients diagnosed with ATTR amyloidosis (inclusive of ATTR-PN and ATTR-CM). To date, limited data are available on the natural history of the hereditary (ATTRm) and wild-type (ATTRwt) forms of the disease, including the regional differences in disease expression by TTR variants and non-mutated TTR, and the genotypic-phenotypic relationship in ATTR amyloidosis.

The principal aims of the outcome survey are to better understand and characterize the natural history of the disease by studying a large and heterogeneous patient population. Survey data may be used to develop new treatment guidelines and recommendations, and to inform and educate clinicians about the management of this disease.

The survey can also generate descriptive safety summaries using adverse and serious adverse event (AE/SAE) data in tafamidis-treated participants. All AE/SAE data will be collected and summarized, including (but not limited to) the safety concerns detailed in Table 1, Summary of Safety Concerns to be Assessed in THAOS.

AE/SAE data collection in THAOS will be utilized in the post-marketing setting to provide additional information on the safety of tafamidis over the long term as well as its effect on survival.

Limited data was collected in ATTR-CM studies with tafamidis in patients with New York Heart Association (NYHA) class IV, and it is expected that THAOS will provide additional information on the safety and efficacy of tafamidis in this population. Safety data will be collected through THAOS for all participants treated with tafamidis.

Additional data corresponding to the events of interest detailed in Table 1 Summary of Safety Concerns to be Assessed in THAOS will also be collected for all THAOS participants (tafamidis-treated and participants not treated with tafamidis). The purpose of the additional data collection is to further characterize the natural history of disease amongst untreated participants and, as applicable, to gather data to provide context for safety events observed amongst tafamidis-treated participants.

### 7.3. Role of THAOS in the Tafamidis European Union Post-Marketing Commitment

On 21 July 2011 the European Union (EU) Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorization for the medicinal product tafamidis 20 mg capsule intended for the treatment of ATTR amyloidosis in adult patients with Stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment. Granting of marketing authorization for tafamidis was made under exceptional circumstances. The collection of safety data in THAOS will fulfill part of the post-marketing commitment to the CHMP for tafamidis. This non-interventional (NI) study is designated as a Post-Authorisation Safety Study (PASS) and is a commitment to the EMA. Additionally, data in ATTR-CM patients collected via this registry will further characterize important potential risks and missing information with tafamidis (see Section 8) as agreed with the EMA during the line extension procedure for ATTR-CM.

## 8. RESEARCH QUESTION AND OBJECTIVES

The objectives of THAOS are to:

- Describe the population of patients affected with ATTR amyloidosis;
- Enhance the understanding of disease natural history, including the variability and progression of the hereditary and acquired forms of the disease;
- Better understand the genotype – phenotype relationship in ATTRm.;
- Compare the progression of disease and overall survival in patients with ATTR with and without liver transplant;
- Foster an international community of medical experts who will develop recommendations on the clinical management of ATTR amyloidosis;
- Provide information to better understand the management and treatment of patients with ATTR amyloidosis through publication of the survey data;

- For tafamidis-treated participants, collect and summarize all AE/SAE data, including for the specific safety concerns outlined in Table 1 Summary of Safety Concerns to be Assessed in THAOS comprising important identified risks, important potential risks, and missing information that includes long-term safety in ATTR-CM patients with NYHA Class IV. For those not treated with tafamidis, collect and summarize additional data on the events of interest listed in Table 1.

# 9. RESEARCH METHODS

## 9.1. Study Design

THAOS is a non-interventional, global, multi-center, longitudinal observational survey open to all patients with ATTR amyloidosis, including both inherited and wild-type forms of disease, and participants with TTR gene mutations without disease diagnosis. There is no set number of patients who will be enrolled. The study has been open since 2007 and will continue until Pfizer declares the study complete (currently estimated to be the year 2023). or as long as patients are able to participate, or until they withdraw consent.

THAOS does not involve the administration of an investigational agent or other intervention. Patients will continue to receive their current medications and all other standard care for their disease. It is recommended that patient assessments be conducted at least annually and recorded in the THAOS electronic data record close to the time they are performed.

Treatment with tafamidis or with other disease modifying therapies will be according to the product label with commercially available product or according to protocol-specified requirements if a participant is enrolled in a tafamidis interventional study.

In addition to routine procedures for standard of care, patients will be asked to complete patient outcome questionnaires at least annually; these are optional and do not affect a patient's eligibility to participate in the survey.

The THAOS electronic data record allows for data to be recorded from an eligibility/baseline visit, at return visits, and in the form of status updates if the patient has not visited the site. In addition, THAOS physicians have the option of recording pre-baseline retrospective patient data. Final data entry (the entry of a status update indicating that the patient has been discontinued) will occur when the survey is completed, if the patient dies, or elects to discontinue the survey.

Physicians at survey sites will evaluate patients to determine eligibility. Each patient must review and sign an informed consent document before any data are recorded in the THAOS electronic data record. The date the informed consent form is signed will be documented in the THAOS electronic data record.

Data will be recorded from all patient visits and entered into the THAOS electronic data record as soon as possible after the visit is complete. Data will be entered into a secure, confidential computer-based application which allows for remote data entry through locally secured connections. A Scientific Board representing the THAOS physicians will meet at least annually and recommend statistical analyses.

Each survey site will be required to obtain local Institutional Review Board (IRB)/Ethics Committee (EC) approval to participate in THAOS and before enrolling patients.

There is no pre-determined number of enrolled patients or participating sites in THAOS. The survey will be conducted at sites worldwide.

### 9.1.1. Study Treatment and Duration

THAOS has been open since 2007. There is no set number of patients who will be enrolled in the survey. Patients will be enrolled from different countries around the world. All patients who take part in this survey will be followed until the survey is declared complete by Pfizer (currently estimated to be the year 2023) or as long as they are able to participate, or until they withdraw consent to participate. For those patients receiving tafamidis, the dosage recommendations (including dosage strength and timing of the dosing) should be based on the prescribing physician's clinical judgment and the approved product label or open-label study protocol (for those patients receiving tafamidis as part of their participation in a clinical study).

## 9.2. Setting

The study population includes patients with confirmed genotyped TTR mutation with or without a diagnosis of hereditary or wild-type ATTR amyloidosis.

Assessments were proposed by a team of experts as components of standard clinical practice for patients with ATTR amyloidosis and are recommended but are not required; the assessments to be performed will be determined by the investigator according to the patient's individual care plan. Additional information on assessments is included in a separate THAOS Case Report Form Completion Guidelines which will be provided to each survey site.

### 9.2.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion into THAOS:

1. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

2. Males and females ≥18 years of age.

3. Confirmed genotyped TTR mutation with or without a diagnosis of hereditary or wild-type ATTR amyloidosis. Confirmation of ATTRwt amyloidosis will be determined by genotyped confirmation that patient does not possess a known mutation in TTR gene (ie, is a carrier of wild-type allele only) via genetic testing and one of the following set of criteria (a, b, or c):

    a. Presence of amyloid in cardiac biopsy tissue confirmed as TTR amyloid by mass spectrometry or immunohistochemistry; or

b. Evidence of cardiac involvement by echocardiogram as defined by left ventricle wall thickness of >12 mm, and presence of amyloid in non-cardiac tissue confirmed as TTR amyloid by mass spectrometry or immunohistochemistry; or

c. No evidence of primary (light chain) amyloidosis, and presence of amyloid in cardiac tissue indirectly confirmed by scintigraphy with a "bone seeking tracer" eg, 99mTC-DPD [99mTC-3,3-diphosphono-1,2-propano-dicarboxylic acid], 99mTC- PYP [Pyrophosphate], and 99mTC-HMDP [hydroxymethylene diphosphonate] with Perugini grade ≥2.

### 9.2.2. Exclusion Criteria

Patients meeting any of the following will not be included in the study:

1. Patient has primary or secondary amyloidosis.

### 9.2.3. Genotyping

TTR genotyping is required to confirm patient eligibility and will be performed before the Eligibility/Baseline visit and outside of the auspices of the survey according to the site's standard practices. For patients with a documented TTR gene mutation, the mutation(s) will be recorded in the patient's medical record and in the electronic data record.

## 9.3. Variables

The objectives of THAOS are to describe the population of patients affected with ATTR amyloidosis and to enhance the understanding of the disease natural history, including the variability and progression of the hereditary and acquired forms of disease.

All visits are intended to be outpatient visits. Assessments are recommended but not required and will be determined by the investigator. All assessments that occur will be recorded in the THAOS electronic data record. The THAOS Electronic Case Report Form Completion Guidelines detail how the data for these assessments should be entered into the electronic data record. Blank worksheets and QoL questionnaires (available in patient's native language) are available to download from the THAOS electronic data record.

### 9.3.1. Study Assessments

- Written informed consent/assent.
- Inclusion/exclusion criteria.
- Patient demographics (year of birth, gender, ethnic origin, race (if allowed by local regulations).
- TTR genetic test results.
- Family disease history (previous family history of ATTR amyloidosis).

- Medical history (past and current signs, symptoms, and medical diagnoses).
- Annual medical assessment (current signs and symptoms).
- General examination (weight/height, vital signs, CCI [redacted]
- Concomitant medications (category, indication, start and stop dates).
- Hospitalizations (admission and discharge dates, reason for hospitalization).
- Transplant history and complications (date(s) of transplant(s), organ(s) transplanted, information on complications).
- AE/SAE reporting for tafamidis-treated subjects.
- Events of interest (as listed in Table 1, Summary of Safety Concerns to be Assessed in THAOS).
- Clinical laboratory data (hematology, clinical chemistry, liver function tests, thyroid function tests).
- Urinalysis (includes glomerular filtration rate [GFR]).
- Cardiovascular assessments (electrocardiogram, echocardiogram, Holter monitoring, CCI [redacted]
- Neurologic assessments (deep tendon reflexes, sensation [pinprick, soft touch, vibration, and position sense], motor strength, nerve conduction studies).
- Eye examination (intraocular pressure, vitreous, presence of opacities).
- Body composition (total bone mineral density and content, total lean and fat mass).
- CCI [redacted]
- Patient death (data on patient death will be collected independently of the visit schedule).

### 9.3.2. Safety Assessments

AE/SAE data collected in THAOS will be used to further characterize the safety profile of tafamidis and as a result, to fulfill certain aspects of the EU post-marketing commitment for tafamidis. Based on the safety concerns detailed in Table 1, corresponding data for Events of Interest will be collected to characterize both the natural history of ATTR in participants not treated with tafamidis and safety concerns amongst tafamidis-treated patients.

**Table 1. *Summary of Safety Concerns to be Assessed in THAOS**

| | |
|---|---|
| Important identified risks (Adverse Drug Reactions) | Urinary tract infection<br>Diarrhea<br>Vaginal infections<br>Upper abdominal pain |
| Important potential risks | Hepatotoxicity<br>Hypersensitivity reactions<br>Reproductive and developmental toxicity and lactation<br>Changes in thyroid function, particularly in pregnant women |
| Important missing information | Safety and efficacy in elderly patients<br>Longer term safety<br>Safety and efficacy in patients with ATTR-PN mutations other than Val30Met<br>Patients with NYHA Class IV<br>Patients with severe hepatic impairment |

Note: *The following important identified risks (Urinary tract infections, Diarrhea, Upper abdominal pain and Vaginal infections); important potential risks (Hypersensitivity reactions); and missing information (Safety and efficacy in elderly patients and Longer-term safety) have been removed from the list of ongoing safety concerns from the tafamidis EU RMP Update (v 9.3), approved on 17 February 2020.

All AE/SAE data will be collected for participants treated with commercially available tafamidis; participants receiving tafamidis as part of their participation in an open-label clinical study will have AE/SAE data collection through the open-label clinical study; reporting of other events in addition to the Events of Interest will be available for participants not treated with tafamidis.

### 9.3.3. Eligibility/Baseline Visit

This visit will be performed to determine a patient's eligibility. It includes obtaining informed consent, chart review to determine eligibility, and recording results of study assessments as outlined in Section 9.3.1 Study Assessments.

### 9.3.4. Return Visit

Return visits will, on average, be conducted annually or more frequently at the discretion of the survey physician. The reporting window for collecting changes in signs, symptoms, AE information, and new diagnoses is from the last prior visit.

### 9.3.5. Retrospective Visit

Any assessments listed in Section 9.3.1 Study Assessments and performed prior to the patient's Eligibility/Baseline visit may be entered into the THAOS electronic data record as retrospective visit data. This data collection is optional.

### 9.3.6. Final Visit

Final visit data collection, including collection of AE/SAE information, will be performed at the completion of the survey, or at the time a patient dies or elects to discontinue from the survey, whichever occurs first. If a patient dies while enrolled in the survey, the site is asked to collect all available information about the patient's death and complete the final visit assessment and patient death case report forms in the THAOS electronic data record.

## 9.4. Data Sources

The THAOS electronic data record allows for data to be recorded from an eligibility/baseline visit, at return visits, and in the form of status updates, if the patient has not visited the site. In addition, THAOS physicians have the option of recording pre-baseline retrospective patient data. Final data entry (the entry of a status update indicating that the patient has been discontinued) will occur when the survey is completed, if the patient dies, or elects to discontinue the survey (refer to Section 9.3.6 above).

## 9.5. Study Size

THAOS has been open since 2007. There is no set number of patients who will be enrolled in the survey. Patients will be enrolled from different countries around the world. All patients who take part in this survey will be followed until the survey is declared complete by Pfizer (currently estimated to be the year 2023) or as long as they are able to participate, or until they withdraw consent to participate.

## 9.6. Data Management

### 9.6.1. Case Report Forms (CRFs)/Data Collection Tools (DCTs)/Electronic Data Record

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

A computer-based application will be used for entering data into the THAOS electronic data record, allowing sites to enter data remotely through locally secured connections. The computer-based application and the data to be collected and entered are described in the THAOS Case Report Form Completion Guidelines which will be provided to each site.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

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

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

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

Prior to initiating the survey, the Sponsor or its designee will train the THAOS physician and site staff to use the THAOS electronic data record and review the THAOS Case Report Form Completion Guidelines. Ongoing technical support will be provided to survey sites by a database development company.

### 9.6.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms. source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to local regulations or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

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

## 9.7. Data Analysis

### 9.7.1. Statistical Methods

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

### 9.7.2. Data Summaries

THAOS data will be available for analysis on 3 different levels: by patient, by individual survey site, and across survey sites.

The primary objective of the survey is to better understand the natural history of ATTR (hereditary and wild-type forms) and the progression of disease in this patient population. Analysis of clinical outcomes will be conducted on all enrolled patients with available data. Outcomes will be examined for the entire patient group, as well as through stratification of important variables that may affect outcomes (for example, but not limited to, TTR variant, age, race, gender, country of origin). Outcomes will include results of the key clinical, functional and QoL assessments used to define progression of disease.

Data will be summarized descriptively and modeled using appropriate statistical methodology.

THAOS physicians may use the THAOS electronic clinical database to obtain ongoing longitudinal data on their individual patients to assist them in following and caring for their patients. A physician can extract their individual survey site data for an individual or all patients enrolled at the survey site to identify trends in the data and/or assist in patient care and monitoring at their survey site.

THAOS physicians may request or share data across survey sites. A request may pertain to available information on patients with a newly identified TTR variant, or on a subset of patients to assist a THAOS physician with the clinical management of a patient (or patients), or to provide information pertinent to research interests across survey sites. Requests for data should be forwarded to the Sponsor for processing and will be promptly reviewed.

### 9.7.3. Scientific Board

The Scientific Board is comprised of a group of scientific and clinical experts in the field of amyloid disease who will provide scientific oversight and interpretation of the data originating from THAOS and its sub-studies. The role of the Board is to develop treatment recommendations and practice guidelines for patients with transthyretin amyloidosis based on findings from either the survey or external data. The roles and responsibilities of the Board are detailed in the THAOS Scientific Board Charter.

### 9.7.4. Interim Analyses

There is no formal interim analysis planned.

Safety data required as part of the European Medicines Agency RMP for tafamidis will be analyzed and submitted annually.

One or more data extracts will be performed annually in order to support ad hoc analyses for publications and for pricing and reimbursement.

## 9.8. Quality Control

### 9.8.1. Data Editing

Data entered into the THAOS electronic clinical database will be automatically checked according to the database specifications, focusing on data critical for analysis, using limits set within the programming. Error messages will appear notifying the sites of discrepancies as they are identified or at the point of data signature. Data clarification requests may be generated and sent electronically to the THAOS sites. Completed requests will be returned to the electronic clinical database. All changes to the THAOS electronic clinical database will be tracked via an audit trail.

### 9.8.2. Audits

Local or international regulatory authorities, the IRB/EC, the Sponsor, or its designee, may request access to all patient consent forms, source documents, THAOS electronic data records, and other survey documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

### 9.8.3. THAOS Electronic Clinical Database

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered in the THAOS electronic clinical database from source documents (eg, hospital or physician patient charts), physical examinations, and patient reports. The investigator must ensure that the information is accurate, authentic/original, attributable, complete, consistent, timely (contemporaneous), enduring, and available when required.

## 9.9. Limitations of the Research Methods

The observational nature of this study has the potential to introduce selection or ascertainment bias. The study population could be more heterogeneous. Confounding leads to biased estimates of associations of risk factors or treatment with outcome and thus impacts the validity of the conclusions from the study. Analytical methods (like matching, multivariate regression) would be used to control for confounding.

Other potential limitations to the validity of the study include missing data and loss to follow-up or censoring. Appropriate statistical methods would be employed to account for missing data and described in the SAP. Sensitivity analysis to assess the impact of loss to follow-up will also be explored.

### 9.10. Other Aspects

Not Applicable.

## 10. PROTECTION OF HUMAN SUBJECTS

### 10.1. Patient Information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

Upon entry into THAOS, a patient will be assigned a unique patient number. This number is a combination of the site country identifier, the assigned site number, and the number given to a patient in order of enrollment at the site (eg, SE 01 005 is the fifth patient enrolled at the first participating site in Sweden). Each patient will be identified by this unique number. In order to maintain patient privacy, all databases, survey reports, and communications will identify the patient only by the unique patient number.

The personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room 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, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

### 10.2. Patient Consent

The informed consent/assent documents and any patient recruitment materials must be in compliance with local regulatory requirements and legal requirements, including applicable privacy laws.

The informed consent/assent documents used during the informed consent process and any patient recruitment materials must be reviewed and approved by Pfizer, approved by the institutional review board (IRB)/independent ethics committee (IEC) before use, and available for inspection.

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

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

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

### 10.2.1. Participation in Investigational Clinical Trials

If a patient in Spain elects to participate in a double-blind or open-label interventional trial, entry of data into THAOS will be prohibited from the date patient begins taking study drug (or device) until the end of the interventional trial. Data collected prior to a patient receiving treatment in a double-blind or open-label interventional trial (eg, baseline, pre-treatment assessments, or any historical data) can be entered into the THAOS electronic data record/database and data collection can resume after completion of the interventional trial. Data collected during the time of participation in an interventional trial may not be entered into THAOS

For patients enrolled outside of Spain, if a patient elects to participate in a double-blind investigational clinical trial, collection of THAOS data will be temporarily suspended during the period that the patient is taking study drug (or device).

Data collected prior to a patient receiving treatment in a double-blind investigational trial (eg, baseline, pre-treatment assessments, or any historical data), as well as data collected after the patient's completion or withdrawal from a double-blind investigational trial, can be entered into the THAOS electronic data record/database. Data collected during the course of the clinical trial may be entered retrospectively at the end of the trial if the THAOS principal investigator obtains and documents approval from the study sponsor who conducted the clinical trial. Retrospective data entry cannot occur until the study has been unblinded,

which will permit identification of the treatment received during the trial. No reconciliation between databases will occur.

As the goal of the survey is to document the course (or natural history) of TTR amyloidosis, the use of known interventions, including open-label investigational agents or devices, will be permitted. For interventional clinical trials that include open-label tafamidis or other open-label investigational products, patients may continue in THAOS, with the approval of the Sponsor, but AE data collection will be addressed through the interventional clinical trial sponsor. The THAOS principal investigator is responsible for obtaining and documenting approval from the study sponsor for investigational agents other than tafamidis.

### 10.3. Patient Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document patient outcome, if applicable. The investigator would inquire about the reason for withdrawal and follow-up with the patient regarding any unresolved AEs.

Whenever possible, the patient should return for a final visit and the reason for withdrawal recorded. If a patient does not return for further assessments and no longer wishes to participate in THAOS, the reason the patient provides for discontinuation from the survey will be recorded. In the event that a patient does not complete an annual visit, can no longer be contacted within one year of a scheduled annual visit, and the patient's status is unknown, the patient will be considered lost to follow-up and the principal investigator (PI) will be required to change the patient status in that individual's THAOS clinical database accordingly.

If the patient withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

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

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

### 10.5. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), EMA European

Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and Food and Drug Administration (FDA) Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data, Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.

## 11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS FOR TAFAMIDIS-TREATED SUBJECTS

### 11.1. Requirements

The table below summarizes the requirements for recording safety events in the THAOS electronic data record and for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) serious adverse events (SAEs); (2) non-serious AEs (as applicable); and (3) scenarios involving drug exposure, including exposure during pregnancy (EDP), exposure during breast feeding, medication error, overdose, misuse, extravasation, and occupational exposure. These events are defined in the section "Definitions of Safety Events"

| Safety event | Recorded in the THAOS electronic data record | Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness |
|---|---|---|
| SAE | All | All |
| Non-serious AE | All | None |
| Scenarios involving exposure to a drug under study, including EDP, exposure during breastfeeding, medication error, overdose, misuse, extravasation; lack of efficacy; and occupational exposure | All (regardless of whether associated with an AE), **except occupational exposure** | All (regardless of whether associated with an AE) |

For each AE, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE (see section "Serious Adverse Events" below).

Safety events listed in the table above must be reported to Pfizer within 24 hours of awareness of the event by the investigator **regardless of whether the event is determined by the investigator to be related to tafamidis.** In particular if the SAE is fatal or life-threatening, notification to Pfizer or its designated representative must be made

immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.

For safety events that are considered serious, or that are identified in the far-right column of the table above, that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded in the THAOS electronic clinical database. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

### 11.2. Reporting Period

For each patient, the safety event reporting period begins at the time of the patient's first dose of tafamidis or the time of the patient's informed consent if s/he is being treated with tafamidis at study start and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of a drug under study; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period.

If a patient was administered a drug under study on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation.

Most often, the date of informed consent is the same as the date of enrollment. In some situations, there may be a lag between the dates of informed consent and enrollment. In these instances, if a patient provides informed consent but is never enrolled in the study (eg, patient changes his/her mind about participation), the reporting period ends on the date of the decision to not enroll the patient.

If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the SAE to be related to tafamidis, the SAE also must be reported to Pfizer Safety.

### 11.3. Causality Assessment

The investigator is required to assess and record the causal relationship.

For all AEs, sufficient information should be obtained by the investigator to determine the causality of each AE. For AEs with a causal relationship to tafamidis, follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that tafamidis caused or contributed to an AE. If the investigator's final determination of causality is "unknown" and the investigator cannot determine whether tafamidis caused the event, then the event will be handled as related to tafamidis for reporting purposes and the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but the investigator determines that tafamidis did not cause the event, this should be clearly documented in the THAOS electronic clinical database and the NIS AEM Report Form.

### 11.4. Definitions of Safety Events

#### 11.4.1. Adverse Events

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an AE);
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Lack of efficacy;
- Drug abuse;
- Drug dependency.

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

- Drug overdose;
- Drug withdrawal;

- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- EDP;
- Exposure during breast feeding;
- Medication error;
- Occupational exposure.

### 11.4.2. Abnormal Test Findings

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

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

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

### 11.4.3. Serious Adverse Events

A SAE is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute AEs);

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

- Results in congenital anomaly/birth defect.

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

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

### 11.5. Hospitalization

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

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported:

- Social admission (eg, patient/subject has no place to sleep);

- Administrative admission (eg, for yearly exam);

- Optional admission not associated with a precipitating medical AE (eg, for elective cosmetic surgery);

- Hospitalization for observation without a medical AE;

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (eg, for work-up of persistent pre-treatment lab abnormality);

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

## 11.6. Scenarios Necessitating Reporting to Pfizer Safety within 24 Hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

### 11.6.1. Exposure During Pregnancy

1. An exposure during pregnancy (EDP) occurs if a female becomes, or is found to be, pregnant either while receiving or having been directly exposed to (eg, environmental exposure) tafamidis, or the female becomes, or is found to be, pregnant after discontinuing and/or being directly exposed to tafamidis (maternal exposure).

2. An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

As a general rule, prospective and retrospective EDP reports from any source are reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed.

If a study participant becomes, or is found to be, pregnant during the study participant's treatment with tafamidis, this information must be submitted to Pfizer, irrespective of whether an adverse event has occurred, using the NIS AEM Report Form and the EDP Supplemental Form, and through the Tafamidis Enhanced Surveillance for Pregnancy Outcomes (TESPO). Reporting to TESPO for women exposed to tafamidis will also include a 6-month and 12-month post-birth follow-up questionnaire regarding developmental milestones.

In addition, the information regarding environmental exposure to tafamidis in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NIS AEM Report Form and the EDP supplemental form. This must be done irrespective of whether an AE has occurred.

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (eg, induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow up to the initial EDP report.

In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

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

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product.

Additional information regarding the EDP may be requested. 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).

### 11.6.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. 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 AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

### 11.6.3. Medication Error

A medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (eg, inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);
- Confusion with regard to invented name (eg, trade name, brand name).

The investigator must submit the following medication errors to Pfizer within 24 hours of awareness, irrespective of the presence of an associated AE/SAE:

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.
- Medication errors including potential medication errors or near misses that do not involve a patient directly. When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:
    - An identifiable reporter;
    - A suspect product;
    - The event medication error.

### 11.6.4. Overdose, Misuse, Extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

### 11.6.5. Lack of Efficacy

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

### 11.6.6. Occupational Exposure

Reports of occupational exposure to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

### 11.7. Single Reference Safety Document

The Core Data Sheet will serve as the single reference safety document during the course of the study, which will be used by Pfizer safety to assess any safety events reported to Pfizer Safety by the investigator during the course of this study.

The Product Label should continue to be used by the investigator for prescribing purposes and guidance.

## 12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

### 12.1. Communication and Publication of Study Results

In the event of any prohibition or restriction imposed (eg, All information in the protocol and other documents provided to the survey physician and survey team are privileged and confidential information. The physician will use this information to accomplish the survey and will not use it for publication without written consent from the Sponsor. It is understood that the survey physician has agreed to provide the Sponsor with data obtained during the survey. The information obtained from the survey may be disclosed to regulatory authority(ies), other investigators, or other parties identified by the Sponsor.

It is anticipated that the survey results will be presented at scientific meetings and/or published in peer-reviewed scientific or medical journals. The Scientific Board will oversee publication of pooled survey results, which will reflect the experience of all participating centers

The Sponsor will retain legal ownership of all data collected from all sites that participate in the survey. Data from each participating site is the property of that participating site. Each participating physician is free to use and publish his or her own data in compliance with the agreement with the Sponsor.

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## 14. LIST OF TABLES



## 15. LIST OF FIGURES

None.

## ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

## ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

This annex is not required.

## ANNEX 3. ADDITIONAL INFORMATION

See Patient Reported Outcome Questionnaires below.

CCI

THAOS
Transthyretin Hereditary Amyloidosis Outcomes Survey
Patient Assessments

Patient no.: | | | | | | | |  Patient Initials:: | | | |

VISIT: | |  Date of Visit: | | | / | | | / | | | |

CCI

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

**1. Mobility**

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

**2. Self-Care**

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

**3. Usual Activities** (*e.g. work, study, housework, family or leisure activities*)

I have no problems with performing my usual activities ☐
I have some problems with performing my usual activities ☐
I am unable to perform my usual activities ☐

**4. Pain/Discomfort**

I have no pain or discomfort ☐
I have moderate pain or discomfort ☐
I have extreme pain or discomfort ☐

**5. Anxiety/Depression**

I am not anxious or depressed ☐
I am moderately anxious or depressed ☐
I am extremely anxious or depressed ☐

CCI

THAOS
Transthyretin Hereditary Amyloidosis Outcomes Survey
Patient Assessments

Patient no.: | | | | | | | |  Patient Initials:: | | | |

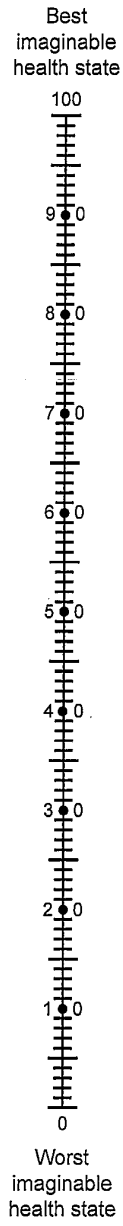
**VISIT:** | |  Date of Visit: | | | / | | | | / | | | |

CCI

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

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

**Your own health state today**



CCI

CCI

| | Feet | Legs | Hands | Arms | None |
|---|---|---|---|---|---|
| 1. Numbness | ❑ | ❑ | ❑ | ❑ | ❑ |
| 2. Tingling, Pins and Needles | ❑ | ❑ | ❑ | ❑ | ❑ |
| 3. Electric Shocks | ❑ | ❑ | ❑ | ❑ | ❑ |
| 4. Other Unusual Sensations | ❑ | ❑ | ❑ | ❑ | ❑ |
| 5. Superficial Pain | ❑ | ❑ | ❑ | ❑ | ❑ |
| 6. Deep Pain | ❑ | ❑ | ❑ | ❑ | ❑ |
| 7. Weakness | ❑ | ❑ | ❑ | ❑ | ❑ |

## Part II: Activities of Daily Life

| Answer these questions according to the following scale: | Not a problem 0 | Very mild problem 1 | Mild problem 2 | Moderate problem 3 | Severe problem 4 |
|---|---|---|---|---|---|
| 8. In the past 4 weeks, has pain kept you awake or woken you at night? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 9. In the past 4 weeks, has the touch of bed sheets, clothes, or wearing shoes bothered you? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 10. In the past 4 weeks, have you burned or injured yourself and been unable to feel it? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 11. In the past 4 weeks, have any symptoms kept you from doing your usual activities during the day? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 12. In the past 4 weeks, have you had difficulty doing fine movements with your fingers, like buttoning your clothes, turning pages in a book, picking up coins from a table? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 13. In the past 4 weeks, have you felt unsteady on your feet when you walk? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 14. In the past 4 weeks, have you had any problem getting out of a chair without pushing with your hands? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 15. In the past 4 weeks, have you had a problem walking down stairs? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 16. In the past 4 weeks, have you been unable to feel your feet when walking? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 17. In the past 4 weeks, have you been unable to tell hot from cold water **with your hands**? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 18. In the past 4 weeks, have you been unable to tell hot from cold water **with your feet**? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 19. In the past 4 weeks, have you had a problem with vomiting, particularly after meals (but not due to flu or other illness)? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 20. In the past 4 weeks, have you had a problem with diarrhea and/or loss of bowel control? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 21. In the past 4 weeks, have you had a problem with fainting or dizziness when you stand? | ❑ | ❑ | ❑ | ❑ | ❑ |

CCI

Protocol ID: _____ CENTER SUBJECT ID

DATE OF VISIT ☐☐ - ☐☐☐ - ☐☐☐☐
dd MMM yyyy

Visit: _____

**KC CARDIOMYOPATHY QUESTIONNAIRE (KCCQ) – Page 1 of 4**

☐ (1) NOT DONE Language administered: ☒ (44) English for USA

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

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

Place an **X** in one box on each line

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

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

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

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

Protocol ID: _____ CENTER SUBJECT ID

DATE OF VISIT dd - MMM - yyyy

Visit: _____

**KC CARDIOMYOPATHY QUESTIONNAIRE (KCCQ) – Page 2 of 4**

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

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

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

It has been...

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

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

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

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

It has been...

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

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

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

Protocol ID: _____ CENTER SUBJECT ID

DATE OF VISIT
dd - MMM - yyyy

Visit: _____

**KC CARDIOMYOPATHY QUESTIONNAIRE (KCCQ) – Page 3 of 4**

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

It has been...

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

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

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

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

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

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

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

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

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

Protocol ID: _____ CENTER SUBJECT ID

DATE OF VISIT dd - MMM - yyyy

Visit: _____

**KC CARDIOMYOPATHY QUESTIONNAIRE (KCCQ) – Page 4 of 4**

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

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

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

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

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

Place an **X** in one box on each line

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

# Document Approval Record

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