Non-Interventional Study Protocol
Protocol B3461001

TRANSTHYRETIN AMYLOIDOSIS OUTCOMES SURVEY (THAOS)

A Global, Multi-Center, Longitudinal, Observational Survey of Patients with Documented Transthyretin (TTR) Mutations or Wild-Type TTR Amyloidosis

Statistical Analysis Plan (SAP)

Version: 3.0

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VERSION HISTORY

Version	Effective Date	Associated Protocol Version	Change Type (New, Revise, Admin)	Summary of Revisions
1.0	09-Feb-2022	Amendment 5 01-Mar-2021	New	NA
2.0	29-Aug-2022	Amendment 5 01-Mar-2021	Revise	Amended to update the analyses sets and subsets based on patient characteristics related to disposition, demographics, efficacy and safety outputs. Inclusion of shift tables of CCI [redacted] Clarification on the phenotype definitions updated. Update on the visit window with +/- 6 months. Minor updates on formatting, typos and layouts.
3.0	27-Jun-2023	Amendment 5 01-Mar-2021	Revise	CCI [redacted] Clarified that sample size in a subgroup needs to be at least 10 in order to have sufficient data to provide descriptive statistics. For all safety events (Concomitant medications, hospitalization, AE/SAE, Deaths, Laboratory, Vitals

				and ECG) all events collected till last tafamidis dosing date +28 days will be summarized for the tafamidis treated set and its associated sub-sets.

1 AMENDMENTS FROM PREVIOUS VERSION(S)

Amendment 1

Section of the SAP	Summary of change	Rationale
2	Spacing issue resolved	Proper formatting
2.1	Added text to include biopsy in assessment of TTR genetic test results. Added text to clarify that complications that will be summarized is related to transplantations. Spacing issue resolved.	Additional clarification for ease of identifying data to be analysed. Proper formatting.
5.3	Added the text "final treatment" corresponding to discontinuation of tafamidis. Added the text "Discontinuation refers to the final treatment discontinuation of tafamidis" in Figure 1. Spelling change of "analyse"	Clarification to highlight that only the last and final date of treatment discontinuation of tafamidis will be considered to identify patients in the tafamidis treated set as there could be multiple discontinuations in THAOS due to the non-interventional nature of this study. Consistency across all sections to use "analyse".
5.4	Revised definitions of the phenotypes with consistent language used in the THAOS ad-hoc publications. Additional text added on classification of patients by liver transplant status for the	To be consistent with the new and updated definitions of phenotypes across all deliverables related to THAOS. The changes in the subgroups with liver transplant in the enrolled

	enrolled patients and the tafamidis treated patients.	set and in tafamidis treated set provides an exhaustive list of all possibilities of either having a liver transplant (prior or after) or no liver transplant.
6.1.2.2	Layout of the second paragraph changed in the form of a sentence from the previous itemized version.	To maintain consistency in formatting with sections 6.1.2.1 and 6.1.2.3.
CCI	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
7	Additional text and corrections on which dates and months to be used for imputing missing dates and specification of the domains for which such imputations will be applied.	To be consistent with the programming standards for imputing missing dates.
8.2	Added the text tafamidis in the last paragraph	To provide clarity that off-label usage corresponds to the study drug tafamidis.
8.2.1	Added text on discontinuation refers to both from the study drug as well as study.	To ensure completeness of summarization of discontinuation either from study drug or study.
8.2.2	Updated the analyses sets to be used for baseline demographics.	To streamline the number of TFLs and make optimum use of the analyses sets and summaries in the best possible way.
8.2.3	Updated the analyses sets to be used for disease characteristics and misdiagnoses. Included the summaries on implantable cardiac	To streamline the number of TFLs and make optimum use of the analyses sets and summaries in the best possible way.

	defibrillator, pacemakers to be presented with the disease characteristics.	
8.2.4	Updated the analyses sets to be used for symptoms.	To streamline the number of TFLs and make optimum use of the analyses sets and summaries in the best possible way.
8.2.5.1	CCI [redacted]	[redacted]
8.2.5.2	CCI [redacted]	[redacted]
8.2.5.3	CCI [redacted]	[redacted]
8.2.6	Updated the analyses sets to be used for survival endpoints and additional text added that only plots will be used for displaying the mortalities.	To streamline the number of TFLs and make optimum use of the analyses sets and summaries in the best possible way.
8.2.7	Updated the analyses sets to be used for exposure.	To streamline the number of TFLs and make optimum use of the analyses sets and summaries in the best possible way.
	Updated the analyses sets to be used for concomitant medications. Added text on how the summaries on concomitant medications will be presented by indication and category.	To streamline the number of TFLs and make optimum use of the analyses sets and summaries in the best possible way. To ease and provide clarity to programming on the representation of

		concomitant medication data.
	Updated the analyses sets to be used for hospitalizations.	To streamline the number of TFLs and make optimum use of the analyses sets and summaries in the best possible way.
	Updated the analyses sets to be used for adverse events and serious adverse events. Additional text to include listings on adverse events for patients with off-label usage of tafamidis and serious adverse events for tafamidis treated set.	To streamline the number of TFLs and make optimum use of the analyses sets and summaries in the best possible way.
	Updated the analyses sets to be used for deaths. Additional text to include listings on deaths for tafamidis treated set.	To streamline the number of TFLs and make optimum use of the analyses sets and summaries in the best possible way.
	Modified text for analyses sets related to summarization of blood pressure and laboratory.	To streamline the number of TFLs and make optimum use of the analyses sets and summaries in the best possible way.
	Updated the analyses sets to be used for ECG.	To streamline the number of TFLs and make optimum use of the analyses sets and summaries in the best possible way.
	Updated the analyses sets to be used for Echocardiogram. Removed the text to summarize data by yearly intervals.	To streamline the number of TFLs and make optimum use of the analyses sets and summaries in the best possible way. Echocardiogram data is only collected at baseline, hence only baseline summaries are applicable.
CCI	[redacted]	[redacted]

		CCI [redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
8.2.8.6	Updated the analyses sets to be used for transplantation.	To streamline the number of TFLs and make optimum use of the analyses sets and summaries in the best possible way.
8.2.8.7	New section added for Phenotype shift tables	The analyses for phenotype shift tables was not explicitly detailed out in the earlier version, hence incorporated in the amendment.
8.2.9	Update on the analyses sets corresponding to different end points	To streamline the number of TFLs and make optimum use of the analyses sets and summaries in the best possible way.
10.2 Appendix 2	Additional text for determination of study day for enrolled analysis/tafamidis untreated set and tafamidis treated set. Update of the visit windows.	To provide clarity in the programming derivation of the study days. The visit window corresponds to the current practice of deriving the visits by applying a 6-month visit window which is based on the earlier

		versions of SAP used for THAOS related analysis.

Amendment 2

Section of the SAP	Summary of change	Rationale
5.4	Revised phenotype classification. Added text to clarity the subgroups to be used for safety and other endpoints. Mixed phenotype will not be combined with any other subgroup.	Refine phenotype classification in alignment with clinical presentation. Clarification to highlight that the sample size in a subgroup needs to be at least 10 in order to have sufficient data to provide descriptive statistics. Clinical presentation, natural history of disease and response to therapy is expected to vary between groups. No scientific rational to present pooled results for mixed combined with any other phenotype.
6.1	CCI [redacted]	[redacted]
6.3	CCI [redacted]	[redacted]
7	Update on handling missing values for proportions.	Patients with missing data for a variable will be excluded from the denominator when calculating proportions

		involving observed data for that variable.
8.1	Update on MMRM and Kaplan-Meier analyses. Clarified sample size requirement for descriptive statistics.	Sufficient data not available to conduct MMRM's in order obtain reliable estimates due to small sample size and high drop-out rate. Sample size in a subgroup needs to be at least 10 in order to have sufficient data to provide descriptive statistics, listings will be provided for smaller subgroups. Kaplan-Meier estimates will be provided if the number of events are at least 5.
8.2.1	Disposition data only to be provided for enrolled patients	Disposition data not needed for treated and untreated cohorts.
8.2.2, 8.2.3, 8.2.4	Add additional variables to be summarized in demographics and disease characteristics table Additional summary on frequency distribution of TTR variants for all enrolled patients. Modification of the text related to symptoms developing post enrolment/baseline.	Demographics: additional variables added – duration of ATTR symptoms at enrollment, time from symptom onset to diagnosis, age at onset of symptoms, follow-up time. Disease characteristics: additional variables added – BMI, mBMI, CCI [redacted] systolic BP, diastolic BP, LV septum, LV ejection fraction, CCI [redacted] Heart failure, abnormal ECG, Atrial fibrillation/flutter,

		participation frequency (%) in tafamidis trial and non-tafamidis trial. As per the nature of the disease, the definition of "new" symptoms is vague and are actually pre-existing symptoms associated with the disease that could onset after enrolment/baseline.
8.2.5, 8.2.7	CCI [redacted] see section 6.1. Updated derivation of duration of exposure to tafamidis.	Descriptive nature of the study limits efficacy analysis. Since a subject may participate in other clinical/compassionate trials while being enrolled in THAOS, the period of such trials needs to be excluded from the safety analysis, including exposure, hence an updated derivation for duration of exposure has been used.
CCI [redacted]	[redacted]	[redacted]
8.2.6	Update on survival analysis.	Moved survival analysis section to safety section in order to be consitant with section 6.2. Kaplan-Meier estimates will be provided if the number of events are at least 5.
8.2.6 (previous section 8.2.7)	Summary on dose increase/decrease/stop to be removed due to limitation in CRF.	The CRF only collects limited information for stopping tafamidis dose which cannot be attributed

		directly to whether dose was increased/decreased.
	Concomitant medications both prior to tafamidis and after tafamidis for treated patients and prior to tafamadis for untreated patients.	Added additional clarification to SAP.
	Added text to safety section: "exposure-adjusted incidence rate". Summary of incidence rates (per patient-year) for AEs and SAE Treatment Emergent Adverse events (All causalities) and mortality for tafamidis treated set" will be provided.	Duration of exposure can be different in the low, high and switched dose groups.
	Hy's law table to be excluded.	Hy's law requires conditions to check whether the lab value is beyond ULN, however THAOS database does not collect records/data on the ULN values for lab parameters.
	Provide duration of exposure listing for patients who switched from 61/80 mg to 20 mg.	Sample is expected to be too small to allow for descriptive statistics. Listing will be provided.
	For all safety events (Concomitant medications, hospitalization, AE/SAE, Deaths, Laboratory, Vitals and ECG) all events collected till last tafamidis dosing date +28 days will be summarized for the tafamidis treated set and its associated sub-sets.	Added additional clarification to SAP.
CCI [redacted]	[redacted]	[redacted]

2 INTRODUCTION

The Transthyretin-Associated Amyloidosis Outcomes Survey (THAOS) is a non-interventional, global, multi-center, longitudinal, observational survey open to all patients with Transthyretin (ATTR) amyloidosis , including both due to TTR variants (ATTRv) and wild-type forms of the disease (ATTRwt), and patients with TTR gene variants (previously referred as mutations) without disease diagnosis. At the inception of THAOS, limited data were available on the natural history of the ATTRv and 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.

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 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 events (AE) and serious adverse events (SAE) data in tafamidis-treated patients. 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 longer term as well as its effect on survival. Additionally, the collection of safety data in THAOS will fulfill part of the post-marketing commitment to the Committee for Medicinal Products for Human Use

(CHMP) for tafamidis. Specifically, this non-interventional (NI) study is designated as a Post-Authorization Safety Study (PASS) and is a commitment to the European Medicine Agency (EMA).

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

The purpose of this statistical analysis plan (SAP) is to support a final study report. Separate statistical analysis plans will be provided for other efforts including but not limited to annual reporting for regulatory requirements, to facilitate reimbursement discussions, and for abstract and/or publication development. Additionally, a separate SAP is available for the B3461029 substudy to evaluate safety and efficacy in transthyretin amyloid polyneuropathy (ATTR-PN) patients with variants other than substitution of methionine for valine at position 30 (Val30Met).

2.1 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 patients with TTR gene variants without disease diagnosis. There is no set number of patients to 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 interventions. Patients will continue to receive their current medications and all other standard care for their disease. It is recommended that 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 patient is enrolled in a separate tafamidis interventional study while simultaneously being followed in THAOS.

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 eligibility to participate in the survey.

Study population

The THAOS study population includes enrolled patients with confirmed ATTRh or ATTRwt amyloidosis and those with a TTR gene variant without a diagnosis of ATTR amyloidosis.

TTR genotyping is required to confirm 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 variant, the variant(s) is recorded in the patient's medical record.

Assessments

A series of assessments will be used to assess disease progression and the effects of tafamidis treatment including demographics, TTR genetic test results,tissue biopsy results, family disease history, medical history, annual medical assessment, general examination, concomitant medication use, hospitalizations, transplant history and complications related to transplantations, AE/SAE reporting for tafamidis-treated patients, health events of interest, clinical laboratory data, urinalysis, CCI [redacted] neurologic assessments, eye examination, body composition, CCI [redacted] and death.

Data will be collected at an eligibility/baseline visit, return visits, and in the form of status updates if the patient has not visited the site. In addition, pre-baseline retrospective data may optionally be captured.

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

A final visit, including collection of AE/SAE information will be performed at the completion of the survey or at the time the patient elects to discontinue, whichever occurs first. For patients enrolled in interventional clinical trials that include open-label tafamidis or other open label investigational products, follow-up in THAOS may continue, but AE data collection and reporting will be addressed through the interventional clinical trial sponsor. If a patient dies while enrolled in the survey, the site is asked to collect all available information related to the death.

If a patient enrolls in a double blind investigational clinical trial or any other trial (including Tafamidis Compassionate Use/Early Access Program) during the course of their follow-up in THAOS, data collected for such patients (if included in the THAOS database) will be excluded from analyses specified within this SAP.

AE/SAE data collected in THAOS will be used to further characterize the safety profile of tafamidis and as a result, to fulfil certain aspects of the European Union (EU) post-

marking commitment for tafamidis. Based on the safety concerns detailed in Table 1, corresponding data for Health Events of Interest will be summarized to characterize both the natural history of ATTR amyloidosis in participants not treated with tafamidis and safety concerns amongst tafamidis-treated patients.

Table 1 Summary of ongoing tafamidis safety concerns to be addressed in THAOS

Level of Risk or Missing Information	Specific Concerns
Important potential risks	Hepatotoxicity Reproductive and developmental toxicity and lactation Changes in thyroid function, particularly in pregnant women
Important missing information	Safety and efficacy in patients with ATTR-PN variants other than Val30Met (B3461029 substudy) CCI [redacted] Patients with severe hepatic impairment

Note: The 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 Risk Management Plan (RMP) Update (v 9.3), approved on 17 February 2020 and therefore will not be addressed in the final clinical study report (CSR) for THAOS.

All AE/SAE data will be collected for patients treated with commercially available tafamidis; patients 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 Health Events of Interest will be available for patients not treated with tafamidis.

All visits are intended to be outpatient visits. Table 2 presents the data collected throughout a patient's participation in THAOS per the case report form (CRF). All assessments listed in Table 2 are recommended, but not required and will be determined by the investigator.

Table 2 Data Collection per Visit

Case Report Form	Eligibility/ Baseline Visit	Return Visits	Retrospective Visits (optional)	Final Visit[c]
Written informed consent/assent	X	--	--	--
Inclusion/exclusion criteria	X	--	--	--

Case Report Form	Eligibility/ Baseline Visit	Return Visits	Retrospective Visits (optional)	Final Visit[c]
Patient demographics date of birth, gender, ethnic origin	X	--	--	--
Clinical trial and compassionate use program participation (log format)	X	X	X	
TTR data genetic test results, tissue biopsy	X	--	--	--
Family history of ATTR amyloidosis	X	--	--	--
Medical history past and current signs, symptoms and medical diagnoses	X	--	--	--
Annual updated medical assessment current signs and symptoms	--	X	--	X
General exam weight/height, vital signs, CCI [redacted]	X	X	X	X
Concomitant medications (log format) category, indication, start and stop dates	X	X	X	X
Tafamidis treatments (log format) dose, start and stop dates	X	X	X	
Hospitalizations (log format) admission and discharge dates, reason for hospitalization	--	X	X	X
Transplant history and complications (log format) date(s) of transplant(s), organ(s) transplanted, information on complications	X	X	X	X
Adverse events	X	X	X	X
Laboratory data Hematology, clinical chemistry, urinalysis, including glomerular filtration rate [GFR]	X	X	X	X
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] *Nerve conduction studies:* Upper Extremity, Lower Extremity	[redacted]	[redacted]	[redacted]	[redacted]
Renal/bladder ultrasound [a] residual volume, number and size of kidneys, echogenicity	X	X	X	X

Case Report Form	Eligibility/ Baseline Visit	Return Visits	Retrospective Visits (optional)	Final Visit[c]
Eye examination [a] intraocular pressure, vitreous, presence of opacities	X	X	X	X
Body composition [a] total bone mineral density and content, total lean and fat mass	X	X	X	X
CCI [redacted]	[redacted]	[redacted]		X
Patient death [b]		X		
Patient discontinuation [b]		X		
Patient status update [b]		X		

[a] Printed assessment worksheets will be available to provide to outside specialists performing assessment(s).
[b] Data on patient deaths, discontinuations, and status assessments will be collected independent of the visit schedule.
[c] The final visit will be considered as the last recorded visit for the patient/patient while being in THAOS. Assessments/concomitant medications/status/safety events/labs recorded on this visit will depend on the availability of the data corresponding to a patient/patient at the final visit and will be analysed as appropriate

2.2 STUDY OBJECTIVES

The objectives of THAOS are to:

- Describe the population of patients affected with ATTR amyloidoses;
- 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 ATTRv;
- Compare the progression of disease and overall survival in patients with ATTR amyloidosis with and without liver transplant;
- Foster an international community of medical experts who will develop recommendations on the clinical management of ATTR amyloidoses;
- Provide information to better understand the management and treatment of patients with ATTR amyloidoses through publication of the survey data;
- Provide information on off-label use of tafamidis by identifying patients who do not meet the inclusion criteria for transthyretin amyloid cardiomyopathy (ATTR-CM)
- For tafamidis-treated patients, 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 CCI Class IV.
- For patients not treated with tafamidis, collect and summarize additional data on the events of interest listed in Table 1.

3 INTERIM ANALYSES

There are no formal interim analyses planned for this study. Safety data required as part of the EMA Risk Management Plan (RMP) for tafamidis will be analysed 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.

A Scientific Board comprised of selected participating physicians, clinical experts and representatives from the Sponsor will oversee data review and analysis of pooled THAOS data collected from all participating sites. The Board will advise on scientific and policy decisions regarding amendments to the survey protocol and publication of THAOS data. Participating physicians may recommend to the Board the addition of specific analyses of data, or new questions to explore based on available results. The roles and responsibilities of the Board are detailed in a separate charter.

4 HYPOTHESES AND DECISION RULES

There are no hypotheses associated with this survey. All analyses will be descriptive.

4.1 STATISTICAL HYPOTHESES

Not applicable for this study.

4.2 STATISTICAL DECISION RULES

Not applicable for this study.

5 ANALYSIS SETS/POPULATIONS

Analysis of clinical outcomes will be conducted on all enrolled patients with available data. Outcomes will be examined for the entire enrolled patient group, as well as through subgroups based on important variables that may affect outcomes (for example, but not limited to, TTR data, phenotype, CCI). Outcomes will include results of the key clinical, functional and Patient Reported Outcome assessments used to define progression of disease.

5.1 ALL ENROLLED

This analysis set will include patients who have been enrolled in THAOS study and have signed the informed consent form.

The enrollment date will be considered as the date when informed consent form (ICF) was signed.

5.2 TAFAMIDIS UNTREATED

The tafamidis untreated set will include the following:

- All available data from patients who have been enrolled in THAOS, signed the informed consent and who have not received tafamidis during the THAOS study.
- All available data before receiving the first dose of tafamidis while in THAOS, for those patients who were not on tafamidis during or after initial enrollment in THAOS but then started receiving tafamidis post enrollment.

Note: Available data after a patient discontinues treatment with tafamidis will be excluded (See Figure 1)

5.3 TAFAMIDIS TREATED

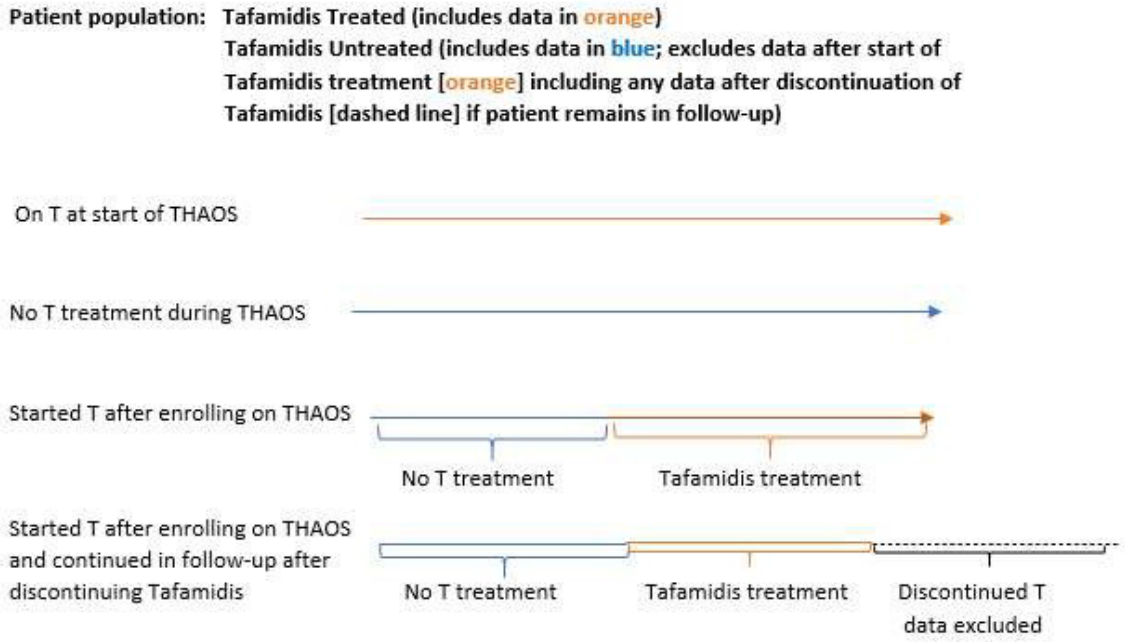
The tafamidis treated set will include the following:

- All available data from the enrollment date until final treatment discontinuation of tafamidis or end of follow-up in THAOS (whichever is earlier) for patients who have been enrolled in THAOS, signed the informed consent and who were on tafamidis treatment on or prior to the date of enrollment in THAOS.
- All available data from first dose of tafamidis until final treatment discontinuation of tafamidis or end of follow-up in THAOS (whichever is earlier) for patients who were not on tafamidis at the time of enrollment in THAOS but subsequently initiated treatment with tafamidis.

Note: A patient can be considered part of both the tafamidis untreated and tafamidis treated sets if the patient initiated treatment with tafamidis after beginning participation in THAOS.

The below schematic will help to better understand the patient population to be analysed:

Figure 1 Schematic of Patient Populations to be analysed



T is denoted as Tafamidis
Discontinuation refers to the final treatment discontinuation of tafamidis

5.4 SUBGROUPS

Subsets/subgroups of the above population, based on patient characteristics, will be used for certain outcomes. Descriptions of key subgroups from THAOS are provided below:

Predominantly Cardiac Phenotype

Predominantly cardiac phenotype includes:

1) Wild type ATTR-CM patients (symptomatic or not) with or without neurologic or gastrointestinal symptoms as follow:

- Neurologic or gastrointestinal (GI) symptoms (erectile dysfunction, constipation, and carpal tunnel) of any severity related or not to ATTR; OR
- Neurologic or gastrointestinal (GI) symptoms (other than erectile dysfunction, constipation, and carpal tunnel) of any severity if unrelated to ATTR; OR
- Neurologic or gastrointestinal (GI) symptoms (other than erectile dysfunction, constipation, and carpal tunnel) of mild severity if related or possibly related to ATTR; AND

- CCI [redacted]

Cardiac and neurologic symptoms do not need to be ongoing at a given visit to be included for phenotyping.

2) Symptomatic ATTRv amyloidosis participants that fulfil the following criteria:

- Presence of abnormal electrocardiogram (ECG) due to rhythm disturbance, heart failure, or dyspnea) of any severity; AND
- Absence of neurologic or gastrointestinal (GI) symptoms (ATTR unrelated, related or possibly symptoms) reported in medical history; AND
- CCI [redacted]

Predominantly Neurologic Phenotype

Predominantly neurologic phenotype includes:

- Symptomatic ATTRv patients with neurologic or GI symptoms of any severity (neurologic and GI symptoms needs to be ongoing and definitely ATTR amyloidosis related); AND
- Absence of abnormal ECG due to rhythm disturbance, heart failure, or dyspnea;

A mPND score ≥ I will be considered a neurologic symptom in this subgroup when reported. Symptomatic patients with missing neurologic and GI symptoms but with a CCI score ≥ I and without abnormal ECG CCI [redacted]

Mixed Phenotype

Mixed phenotype includes:

1) Wild type participants with:

- Any neurologic or GI symptoms excluding Erectile dysfunction/constipation/carpal tunnel syndrome of moderate or severe intensity that are classified as related or possibility related to ATTR;

A mPND score ≥ I will qualify the participant as mixed phenotype independent of the presence of other neurological or GI symptoms.

2) Symptomtatic ATTRv amyloidosis participants that fulfil the following criteria:

- Abnormal ECG due to rhythm disturbance, heart failure, or dyspnea, AND
- Any ongoing neurologic or GI symptoms including erectile dysfunction, constipation, carpal tunnel syndrome of any severity, AND / OR
- A mPND score ≥ I

Mixed phenotype will not be combined with any other phenotype when analyzing the data.

Asymptomatic

Participants with a ATTR variants that are asymptomatic and either have a CCI score <I or missing.

Unclassified Phenotype

Participants who do not qualify as predominately cardiac, neurologic, mixed phenotype or are asymptomatic.

Additional details about the phenotypes can be found in Table 3 below.

Table 3: Phenotype classification

Phenotype	Genotype	Symptomatic	Cardiac symptoms with medical history= "cardiovascular"	Cardiac symptoms ongoing status	Cardiac symptom severity	Neurologic symptoms with medical history= "Neurologic" or "GI"	Neurologic symptoms ongoing status	Neurologic symptoms severity	mPNDscore
Predominantly cardiac	ATTRwt	Yes/ No	Rhythm disturbance/Heart failure/Dyspnoea	Either ongoing or not ongoing	Any severity	Erectile dysfunction/constipation/carpal tunnel syndrome	Ongoing/or not	Any severity related or not	< I or missing
	ATTRwt	Yes/ No	Rhythm disturbance/Heart failure/Dyspnoea	Either ongoing or not ongoing	Any severity	Any neuro/GI symptoms other than Erectile dysfunction/constipation/carpal tunnel syndrome	Ongoing /or not	Any severity if unrelated, or Mild related, possibly related	< I or missing
	ATTRv	Yes	**Rhythm** disturbance/Heart failure/Dyspnoea	Either ongoing or not ongoing	Any severity	No neuro or GI TTR related or possibly symptoms	none	none	< I or missing
Predominantly neurologic	ATTRv	Yes	Any cardiac symptoms except Rhythm disturbance/Heart failure/Dyspnoea or No cardiac symptoms	Either ongoing or not ongoing	Any severity	Any neuro/GI symptoms including Erectile dysfunction/constipation/carpal tunnel syndrome	Ongoing	Any	I or Missing
	ATTRv	Yes	Any cardiac symptoms except Rhythm disturbance/Heart failure/Dyspnoea or No cardiac symptoms	Either ongoing or not ongoing	Any severity	Missing	Missing	Missing	I

Mixed	ATTRwt	Yes	Rhythm disturbance/Heart failure/Dyspnoea	Either ongoing or not ongoing	Any severity	Any neuro/GI symptoms excluding Erectile dysfunction/constipation/carpal tunnel syndrome	Ongoing	Moderate/Severe related related or possibility related	I or missing with symptons as described
	ATTRv	Yes	Rhythm disturbance/Heart failure/Dyspnoea	Either ongoing or not ongoing	Any severity	Any neuro/GI symptoms including Erectile dysfunction/constipation/carpal tunnel syndrome	Ongoing	Any	I or missing (if missing must have symptoms as described)

The other subgroups to be considered are as follows:

- CCI [redacted]
- Severe hepatic impairment (only to be used corresponding to tafamidis treated set). The patients with severe hepatic impairment at baseline will be identified by any of the following:
    - The following pre-coded terms on the Gastrointestinal medical history and the Gastrointestinal general assessment forms: Hepatitis, Cirrhosis, Gastrointestinal malignancy, Hepatotoxicity, Other hepatic impairment having severity scale as "severe".
    - The following terms appearing in the database as entered on the Other Gastrointestinal Medical History or General Assessment forms at baseline and assessed as 'severe': "severe impaired hepatic function", "severe hepatic dysfunction", "severe liver dysfunction/liver failure". Other similar terms as identified during the final database lock of this study may be investigated to identify patients with severe hepatic impairment at baseline.
- Patients not on tafamidis at the time of enrollment on THAOS who had a liver transplant prior to enrollment on THAOS
- Patients not on tafamidis at the time of enrollment on THAOS who had a liver transplant after enrollment on THAOS
- Patients not on tafamidis at the time of enrollment on THAOS without any liver transplant either before or after enrollment on THAOS
- Patients treated with tafamidis at any time in THAOS and with a liver transplant prior to first dose of tafamidis
- Patients treated with tafamidis at any time in THAOS and with a liver transplant after the first dose of tafamidis
- Patients treated with tafamidis at any time in THAOS and never had a liver transplant
- Off-label use of 80/61 milligram (mg) of tafamidis (only to be used corresponding to tafamidis treated set) defined as:
    - Patients not classified as predominantly cardiac or mixed phenotype at the first date of dosing with a dose of 80/61 milligram (mg) of tafamidis.
- Predominantly neurologic at baseline who become mixed phenotype post baseline*
- Predominantly cardiac at baseline who become mixed phenotype post baseline*

Sample size in a subgroup needs to be at least 10 in order to have sufficient data to provide descriptive statistics, listings will be provided for smaller subgroups.

***Changes of phenotype**

Under the assumption that phenotype-related symptoms do not truly disappear, but are only possibly masked or temporarily resolved, once determined, phenotype classification

will be carried forward to future visits even if there are no available symptom data at the subsequent visit. Patients classified as predominantly cardiac or predominantly neurologic at a given visit will continue to be classified as such at subsequent visits unless the patient develops additional symptoms warranting a re-classification to mixed phenotype. Missing data on prior visit will disqualify re-classification (participant must have data entered in the same measure to allow comparison and reclassification). The mixed phenotype is a persistent state, i.e, once a patient is classified as mixed phenotype at a given visit, then that patients remains mixed at all subsequent visits.

For those patients who initiated treatment with tafamidis after beginning participation in THAOS, phenotype treatment baseline will be the most recent phenotype classification prior to first dose.

6 ENDPOINTS AND COVARIATES

6.1 EFFICACY ENDPOINTS

All efficacy endpoints in this study are conisdered CCI (see section 6.3).

6.2 SAFETY ENDPOINTS

All AE/SAE data will be summarized, including (but not limited to) the safety concerns detailed in Table 1 Summary of Ongoing Safety Concerns to be Assessed in THAOS: hepatotoxicity, changes in thyroid function (particularly in pregnancy); reproductive and developmental toxicity and lactation.

Safety endpoints include the incidence of AEs and SAEs, change from baseline in laboratory parameters and change from baseline in vital signs.

For interventional clinical trials that include open-label tafamidis or other open label investigational products, patients may continue in THAOS, but data collected for such patients (if included in the THAOS database) will be excluded from all safety analyses specified within this SAP.

6.2.1 Survival

Survival will be analysed as time from enrollment or first dose of tafamidis, for the untreated and tafamidis treated set respective until the time of death. Patients who are still alive at the end of the analysis period (start of tafamidis or end of follow-up in THAOS for the untreated set or last dose of tafamidis in the tafamidis treated set) will be censored.

CCI

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- [redacted]
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CCI

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CCI [redacted]

CCI [redacted]

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CCI [redacted]

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- [redacted]
- [redacted]

[redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

7 HANDLING OF MISSING VALUES

Missing observations will be treated as missing except for dates. For dates with missing days but not missing months, the 1st of the month will be imputed, and for dates with missing months and days, July will be imputed for months and the 15th will be imputed for days.

For any missing data (CCI [redacted] corresponding to PRO, the PRO specific scoring manual will be utilized for imputation.

Patients with missing data for a variable will be excluded from the denominator when calculating proportions involving observed data for that variable.

If the tafamidis start day is missing, it will be imputed as the 15th of the corresponding month as per the eCRF guidelines. For date of birth, if only year is collected, then the day and month will be considered as 1st of January.

8 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1 STATISTICAL METHODS

The key objectives of the survey are 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 separately for the untreated and tafamidis treated sets, as well as for appropriate subgroups within these set. Outcomes will include results of the key clinical, functional and QoL assessments used to define progression of disease.

Data will be summarized descriptively.

Continuous variables will be summarized using descriptive statistics ie, number of non-missing values and number of missing values [ie, n (missing)], mean, median, standard deviation (SD), minimum, maximum and 10th and 90th percentile.

Qualitative variables will be summarized by frequency counts and percentages. Unless otherwise specified, the calculation of proportions will be based on non-missing values.

In case the analysis refers only to certain visits, percentages will be based on the number of patients still present in the study at that visit, unless otherwise specified. Sample size in a subgroup needs to be at least 10 in order to have sufficient data to provide descriptive statistics, listings will be provided for smaller subgroups.

Kaplan-Meier estimates (product-limit estimates) will be presented including the median time with two-sided 95% confidence intervals (CIs), if the number of events are at least 5.

8.2 STATISTICAL ANALYSES

The baseline visit will be considered as the last available visit on or before the date of sign of informed consent form for the all-enrolled set and the untreated set (as well as any other subgroups corresponding to this untreated set). For the treated set (as well as any other subgroups corresponding to this treated set), the baseline will be considered as the last available value within 3 weeks prior to or 3 weeks after starting tafamidis.

For the subgroup of patients with off-label use, the baseline will be the last available value prior to receiving the first dose of tafamidis 80/61 mg.

8.2.1 Disposition

Disposition status, along with reasons for discontinuation (from treatment as well as study) will be summarized by number and percentage of patients for the all enrolled patients.

8.2.2 Baseline demographics

Summaries of baseline demographic will include the following:
Gender, age at enrollment, race/ethnicity, country of birth, country of residence, country of origin, duration of ATTR amiloydosis symptoms at enrollment, time from symptom onset to diagnosis, age at onset of symptoms, follow-up time.

Summaries will be provided for the following sets: all enrolled patients, tafamidis treated set by phenotype at enrollment and overall, tafamidis untreated set by phenotype at enrollment and overall.

8.2.3 Disease characteristics

Summaries of disease characteristics will be provided for the following sets: all enrolled patients, tafamidis treated set by phenotype at enrollment and overall, tafamidis untreated set by phenotype at enrollment and overall.

Summaries will include CCI score at baseline, CCI [redacted] whether or not the patient was diagnosed with ATTR amyloidosis, time since symptom onset, time since diagnosis, age at onset of symptoms, how diagnosis was made (symptoms, amyloid confirmed on biopsy, TTR confirmed as precursor protein, scintigraphy, other), prior misdiagnosis (Y/N), genotype (TTR mutation vs wild type), diagnosis type for the wild type subset, past or current clinical trial participation (Y/N), past or current Tafamidis Compassionate Use/Early Access or other non-commercial program (Y/N), family history (Y/N; as well as details – inherited from, method of diagnosis in affected family member, number of affected generations), number and percentage of patients with pacemakers at baseline, with the indication and type, number and percentage of patients with implantable cardiac defibrillator at baseline with indication (primary prevention of sudden death (Y/N), secondary prevention of sudden [redacted] CCI [redacted] CCI [redacted] Heart failure, abnormal ECG, Atrial fibrillation/flutter, participation frequency (%) in tafamidis trial and non-tafamidis trial.A summary of misdiagnoses will also be provided for the following sets: all enrolled patients, tafamidis treated set by phenotype at enrollment and overall, tafamidis untreated set by phenotype at enrollment and overall.

8.2.4 Symptoms

The ongoing definitely related symptoms at enrollment/baseline, ongoing possibly related symptoms at enrollment/baseline, and ongoing symptoms at enrollment/baseline unrelated to TTR will be summarized by severity for the following sets: tafamidis treated set by phenotype at enrollment and overall, tafamidis untreated set by phenotype at enrollment and overall, and tafamidis treated set who are either predominantly cardiac or mixed phenotype at enrollment by CCI class at enrollment.

The past definitely related symptoms at enrollment/baseline, past possibly related symptoms at enrollment/baseline, and past symptoms at enrollment/baseline unrelated to TTR will be summarized by severity for the following sets: tafamidis treated set by phenotype at enrollment and overall, tafamidis untreated set by phenotype at enrollment and overall.

Symptoms developed post enrollment/baseline (defined as a symptom with an onset date after the date of enrollment for the untreated set and as a symptom with an onset date after the first dose of tafamidis for the treated subset) will be summarized by severity separately based on whether or not symptoms were definitely related, possibly related, or unrelated to TTR for the following sets: tafamidis treated set by phenotype at enrollment and overall, tafamidis untreated set by phenotype at enrollment and overall, tafamidis treated set who are either predominantly cardiac or mixed phenotype at enrollment by CCI class at enrollment, tafamidis treated set for patients who switched from predominantly cardiac to mixed phenotype, tafamidis treated set for patients who switched from predominantly neurologic to mixed phenotype, tafamidis untreated set for patients who switched from predominantly cardiac to mixed phenotype, tafamidis untreated set for patients who switched from predominantly neurologic to mixed phenotype.

8.2.5 Efficacy Analyses

There are no specific efficacy endpoints collected in this study only safety and CCI , see sections 6.2 and 6.3.

8.2.6 Safety Analyses

Survival Analyses
Mortality will be analysed using the Kaplan Meier method with median survival times (if estimable) and 95% Cis if the number of events are at least 5.

Mortality will be summarized and presented by plots for the following sets: tafamidis treated set by phenotype at enrollment and overall, tafamidis untreated set by phenotype at enrollment and overall, CCI and either predominantly cardiac or mixed phenotype at enrollment, tafamidis treated set for patients who had severe hepatic impairment at baseline, tafamidis

untreated set by their liver transplantation status (liver transplant prior to enrollment/liver transplant after enrollment/no liver transplant), tafamidis treated set by liver transplantation status (liver transplant prior to first dose of tafamidis/liver transplant after the first dose of tafamidis/no liver transplant).

Exposure

Duration of exposure (in years) among patients receiving tafamidis while enrolled in THAOS will be summarized (excluding time when the patient was part of clinical trial or Compassionate Use/Early Access Program) by starting dose using the tafamidis treated set by phenotype at enrollment and overall, CCI and either predominantly cardiac or mixed phenotype at enrollment, tafamidis treated set for patients who had severe hepatic impairment at baseline, tafamidis treated set by liver transplantation status (liver transplant prior to first dose of tafamidis/liver transplant after the first dose of tafamidis/no liver transplant).

Additionally the duration of treatment with 20 mg and 61 mg/80 mg will be summarized separately for patients with off label use.

The duration of exposure (in years) will be calculated as:

Sum of all non-missing days when tafamidis was taken (excluding days of other clinical trial/compassionate use participation) / 365.25

Summary of exposure-adjusted Incidence rates (per patient-year) AEs and SAE for Treatment Emergent Adverse events (All causalities) and mortality for tafamidis treated set will be provided.

A seperate listing will be provided for duration of exposure listing for patients who switched from 61/80 mg to 20 mg.

Concomitant Medications

Summary on concomitant medications by indication and category both prior to and after tafamadis will be provided using the tafamidis treated set by phenotype at enrollment and overall and prior to tafamidis for untreated set by phenotype at enrollment and overall.

Hospitalization

Summary on the frequency of all hospitalizations, the frequency of ATTR related hospitalizations and the reasons for hospitalizations will be summarized using the tafamidis treated set by phenotype at enrollment and overall, tafamidis untreated set by phenotype at enrollment and overall, CCI

CCI and either predominantly cardiac or mixed phenotype at enrollment.

Adverse Events & Serious Adverse Events

All adverse events will be coded according to the latest Medical Dictionary for Regulatory Activities (MedDRA) version at the time of analysis.

Adverse events (all causality and treatment-related) will be summarized by severity and starting dose using the tafamidis treated set by phenotype at enrollment and overall, CCI and either predominantly cardiac or mixed phenotype at enrollment, tafamidis treated set for patients who had severe hepatic impairment at baseline, tafamidis treated set by liver transplantation status (liver transplant prior to first dose of tafamidis/liver transplant after the first dose of tafamidis/no liver transplant).

Separate summaries will be provided for all AEs, treatment related AEs, all SAEs, treatment related SAEs, AEs leading to dose reduction, AEs leading to withdrawal of tafamidis (temporarily or permanently, or delayed) and AEs leading to tafamidis dose interruptions.

Listings will be provided for adverse events corresponding to all enrolled patients and for patients with off-label usage of tafamidis. A separate listing of SAEs will also be provided for tafamidis treated set.

The following AE summary tables will be provided corresponding to some of the important potential risks using the tafamidis treated set.

- For **hepatotoxicity** using the search criteria: MedDRA SMQ (Standardized MedDRA Query) [Broad and narrow] Drug related hepatic disorders – comprehensive search. The derivations and conventions related to the search criteria will follow the programming specifications done in the Periodic Safety Update Report (PSUR) 12 for tafamidis.
- For **reproductive and developmental toxicity and lactation**:
    - MedDRA SMQ (Broad and narrow): Congenital, familial and genetic disorders; Foetal disorders; Neonatal disorders, Neonatal exposures via breast milk.
    - MedDRA Preferred terms (PTs): Exposure during pregnancy, Exposure via father, Foetal exposure during delivery, Foetal exposure during pregnancy, Foetal exposure timing unspecified, Maternal exposure before pregnancy, Maternal exposure during delivery, Maternal exposure during pregnancy, Maternal exposure timing unspecified, Drug exposure before

pregnancy, Exposure via breastmilk, Maternal drug affecting foetus, Maternal exposure during breastfeeding
    - The derivations and conventions related to the search criteria will follow the programming specifications done in the PSUR 12 for tafamidis.
- For **changes in thyroid function,** using the search criteria: MedDRA SMQ (Broad and narrow): Thyroid dysfunction. The derivations and conventions related to the search criteria will follow the programming specifications done in the PSUR 12 for tafamidis.
- For **off-label use**, MedDRA PTs: product use in unapproved indication, Product use issue, Intentional product use issue, Drug effective for unapproved indication, Drug ineffective for unapproved indication

Deaths

Summaries on the number (%) of patients who died, by primary cause, and whether deaths were ATTR related will be provided using all enrolled patients, tafamidis treated set by phenotype at enrollment and overall, tafamidis untreated set by phenotype at enrollment and overall, CCI [redacted] and either predominantly cardiac or mixed phenotype at enrollment, tafamidis treated set for patients who had severe hepatic impairment at baseline, tafamidis treated set by liver transplantation status (liver transplant prior to first dose of tafamidis/liver transplant after the first dose of tafamidis/no liver transplant), tafamidis untreated set by their liver transplantation status (liver transplant prior to enrollment/liver transplant after enrollment/no liver transplant).
A separate listing of deaths will also be provided for the tafamidis treated set.

Hematology and Chemistry

Change from baseline by yearly intervals of the hematology and biochemistry laboratory parameters will be provided using the tafamidis treated set by starting dose.

Blood Pressure

Change from baseline by yearly intervals of the systolic and diastolic blood pressure will be provided using tafamidis treated set by starting dose and tafamidis untreated set.

Electrocardiogram

For ECG, the following summaries will be provided at baseline and by yearly intervals:
- Any abnormalities in rhythm (Y/N)
- Sinus pause (Y/N)
- Atrial flutter (Y/N)

- Atrial fibrillation (Y/N)
- Atrial premature beat (Y/N)
- Junctional rhythm (Y/N)
- Ventricular tachycardia (Y/N)
- Ventricular premature complexes (Y/N)
- Other rhythm abnormality (Y/N)
- Pacemaker with normal function (Y/N)
- Low voltage (Y/N)
- Conduction abnormalities(Y/N)
- Types of conduction abnormalities
- Morphology abnormalities
- Types of morphology abnormalities
- Pathologic Q-Waves observed
- Types of P-Q wave abnormalities
- ST Segment T Wave abnormalities
- Types of ST Segment abnormalities

Also for the following parameters corresponding to ECG, summary statistics for the baseline and change from baseline by yearly intervals will be provided:

- QRS Axis
- PR
- QRS
- QT
- QTc

The summaries will be done using the tafamidis untreated set with predominantly cardiac or mixed phenotype at enrollment, tafamidis treated set with predominantly cardiac or mixed phenotype at enrollment, CCI and either predominantly cardiac or mixed phenotype at enrollment, tafamidis treated set for patients who switched from predominantly neurologic to mixed phenotype and tafamidis untreated set for patients who switched from predominantly neurologic to mixed phenotype.

Echocardiogram

For Echocardiogram, summary statistics for the baseline will be provided for:

- Left atrium
- Aortic root
- LV septum
- LV posterior wall

- LV diastolic diameter
- LV systolic diameter
- LV ejection
- RV free wall thickness
- Quantitative LV end systolic volumes
- Quantitative LV end diastolic volumes
- Transmitral E wave peak velocity
- E wave deceleration time
- Transmitral A wave Peak velocity
- Peak tricuspid regurgitation velocity
- Derived peak pulmonary artery systolic pressure
- Septal and Lateral Peak E, A, S
- Stroke volume
- Cardiac output

Also for the following parameters corresponding to Echocardiogram, summaries will be provided at baseline:

- Value abnormalities
- Types of value abnormalities
- Respiratory variation
- Sparkling

Echocardiogram summaries will be performed for the following sets: tafamidis untreated set with predominantly cardiac or mixed phenotype at enrollment, tafamidis treated set with predominantly cardiac or mixed phenotype at enrollment, CCI [redacted] and either predominantly cardiac or mixed phenotype at enrollment, tafamidis treated set for patients who switched from predominantly neurologic to mixed phenotype and tafamidis untreated set for patients who switched from predominantly neurologic to mixed phenotype.

Note: For all the above safety events (Concomitant medications, hospitalization, AE/SAE, Deaths, Laboratory, Vitals and ECG) all events collected till last tafamidis dosing date +28 days will be summarized for the tafamidis treated set and its associated sub-sets.

CCI [redacted]

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[redacted]

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CCI [redacted]

[redacted]

8.2.8 Summary of Analyses

Data	All enrolled	Untreated overall & by phenotype	Untreated predominantly neurologic/mixed	Untreated predominantly cardiac/mixed	Treated Overall and by phenotype	Treated predominantly neurologic/mixed	Treated predominantly cardiac/mixed	Treated by starting dose	[redacted]	[redacted]	Treated severe hepatic impaired at baseline	Patients not on tafamidis at the time of enrollment with a liver transplant prior to enrollment on THAOS	Patients not on tafamidis at the time of enrollment with a liver transplant after enrollment on THAOS	Patients not on tafamidis at the time of enrollment with no liver transplant	Treated with liver transplant prior to first dose of tafamidis in the study	Treated with liver transplant after first dose of tafamidis in the study	Treated with no liver transplant either prior to first dose of after first of tafamidis in the study	Treated with off-label usage	Untreated predominantly neurologic who become mixed	Untreated predominantly cardiac who become mixed	Treated predominantly neurologic who become mixed	Treated predominantly cardiac who become mixed
Disposition	x																					
Demography	x	x			x																	
Disease Characteristics	x	x			x																	
Misdiagnoses	x	x			x																	
Ongoing symptoms by ATTR relatedness (definite/possibly related/unrelated)		x			x				x													
Past symptoms by ATTR relatedness (definite/possibly related/unrelated)		x			x																	
New symptoms by ATTR		x			x				x										x	x	x	x

CCI [redacted]				x			x		x		x							x		x	
[redacted]				x			x		x												
[redacted]			x			x						x	x	x					x		x
Survival		x			x					x	x	x	x	x	x	x	x				
Exposure to Tafamidis					x			x		x	x				x	x	x				
Concomitant medications		x			x																
Hospitalizations		x			x					x											
AE/SAE					x			x		x	x				x	x	x	x			
Death	x	x			x					x	x	x	x	x	x	x	x				
Labs – baseline and change from baseline		x			x			x													
Hy's Law					x			x													

Blood pressure – baseline and change from baseline	x	x			x																
ECG				x			x			x									x		x	
ECHO				x			x			x									x		x	
CCI		x			x																	
[redacted]			x			x																
[redacted]			x			x																
[redacted]			x			x																
[redacted]				x			x		x										x		x	
[redacted]				x			x															
Transplant		x			x																	
[redacted]		x			x																	

Phenotype shift from enrollment		X			X																

9 REFERENCES

1. Bril V. NIS-LL: The primary measurement scale for clinical trial endpoints in diabetic peripheral neuropathy. Eur Neurol 1999;41(suppl 1);8-13.
2. B3461001 Study Protocol Amendment 5, 17 January 2020

10 APPENDICES

APPENDIX 1: LIST OF ABBREVIATIONS

CCI	[redacted]
ADL	activities of daily living
AE	adverse events
ANCOVA	analysis of covariance
ATTR	Transthyretin amyloid protein
ATTR-CM	transthyretin amyloid cardiomyopathy
ATTRv	ATTR due to a variant
ATTR-PN	transthyretin amyloid polyneuropathy
ATTRwt	ATTR wild type
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CRF	case report form
CSR	clinical study report
ECG	electrocardiogram
EMA	European Medicine Agency
CCI	[redacted]
EU	European Union
GFR	glomerular filtration rate
GI	gastrointestinal
ICD	implantable cardiac defibrillator
ICF	informed consent form
CCI	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MMRM	Mixed model repeated measures
CCI	[redacted]
MRC	Medical Research Council
NI	Non-interventional
CCI	[redacted]

CCI [redacted]	[redacted]
[redacted]	
PASS	Post-Authorization Safety Study
PSUR	Periodic Safety Update Report
PT	Preferred term
QoL	Quality of Life
QTcF	corrected QT (Fridericia method)
RMP	Risk Management Plan
ROM	Range of Motion
SAE	serious adverse events
SAP	statistical analysis plan
SD	Standard deviation
SMQ	Standardized MedDRA Query
TFL	Tables, Figures and Listings
THAOS	The Transthyretin-Associated Amyloidosis Outcomes Survey
TQoL	Total quality of Life
TTR	Transthyretin
Val30Met	Substitution of methionine for valine at position 30
VAS	visual analogue scale

APPENDIX 2: DATA DERIVATION DETAILS

A1.1 Definition and use of visit windows in reporting

For All enrolled set and tafamidis untreated set (as well as the subgroups corresponding to untreated set), Day 1 will be the most recent available value collected either on or after the informed consent signed date. The study day will be calculated as follows:

Study day = assessment date – consent date

For the tafamidis treated set (as well as the subgroups corresponding to treated set), Day 1 will be the most recent available value collected either on or after the first dose of tafamidis received after enrollment in THAOS. The study day will be calculated as follows:

Study day = assessment date – date of first dose of tafamidis after enrollment in THAOS / consent date if patient was continuing taking tafamidis prior to enrollment (whichever is earlier) + 1

The following visit window will be applied, considering the absolute value of study day (absday):

Condition	Visit	Year
absday < -365.25 × 0.5	-1	
0 ≤ absday ≤ 365.25 × 0.5	0	
365.25 × 0.5 < absday ≤ 365.25 × 1.5	1	1
365.25 × 1.5 < absday ≤ 365.25 × 2.5	2	2
365.25 × 2.5 < absday ≤ 365.25 × 3.5	3	3
365.25 × 3.5 < absday ≤ 365.25 × 4.5	4	4
365.25 × 4.5 < absday ≤ 365.25 × 5.5	5	5
365.25 × 5.5 < absday ≤ 365.25 × 6.5	6	6
365.25 × 6.5 < absday ≤ 365.25 × 7.5	7	7
365.25 × 7.5 < absday ≤ 365.25 × 8.5	8	8
365.25 × 8.5 < absday ≤ 365.25 × 9.5	9	9
365.25 × 9.5 < absday ≤ 365.25 × 10.5	10	10
365.25 × 10.5 < absday ≤ 365.25 × 11.5	11	11
365.25 × 11.5 < absday ≤ 365.25 × 12.5	12	12

Note: If study day is missing, then visit will be considered as missing.

CCI [redacted]