NON-INTERVENTIONAL (NI) DRUG STUDY PROTOCOL

A THAOS SUB-STUDY EVALUATING THE EFFECTS OF TAFAMIDIS ON DISEASE PROGRESSION IN PATIENTS WITH NON-V30M MUTATIONS AND SYMPTOMATIC NEUROPATHY

Compound Number:	PF-0691826
Compound Name:	Tafamidis meglumine
Study Number:	B3461029
Version and Date:	Final 30 September 2011

SCHEDULE OF ACTIVITIES

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

Schedule of Study Procedures – Protocol B3461029

	Standard of Care Period[1]			Tafamidis Treatment Period			
	Baseline (Day 0)	**Month 6**	**Additional every 6 month visits (as needed)**	**Initiation of Tafamidis Treatment[2]**	**Month 18**	**Month 24**	**Early Termination/ End of Study**
Informed consent	X						
Genotyping	X						
Eligibility review and start date of tafamidis therapy	X			X			
Medical history (including hospitalizations)	X						
General examination (weight/height, vital signs, Karnofsky Performance Index)	X	X	X	X	X	X	X
Serum albumin (for mBMI) and liver function tests, thyroid function tests, transthyretin, urine β-hCG	X	X	X	X	X	X	X
Motor Function (MRC Scale)	X	X	X	X	X	X	X
Sensory perception and Reflexes	X	X	X	X	X	X	X
Norfolk QOL-DN and EQ5D	X	X	X	X	X	X	X
Modified polyneuropathy (walking) disability score (mPND)	X	X	X	X	X	X	X
ECG and ECHO	X		X	X		X	X
Adverse event and serious adverse event reporting[3]		X (on-going)					
Health events of interest: • Urinary tract infection • Diarrhea • Vaginal infections • Upper abdominal pain • Hepatotoxicity • Thyroid dysfunction		X (on-going)					
Concomitant medications		X (on-going)					
End of Study Form							X

1. Note that the duration of the standard of care period may vary, depending on commercial availability of tafamidis. Regardless of duration of the period, visits should be scheduled every 6 months. The standard of care period for this study may be completed with prior THAOS participation.
2. Initiation of tafamidis treatment will be per PI discretion upon commercial availability of tafamidis in the country of residence for the patient. Initiation of treatment with tafamidis may occur less than 6 months after prior visit within this substudy.
3. All adverse event and serious adverse event data will be collected for participants treated with commercially available tafamidis; participants receiving tafamidis as part of their participation in an open-label study will have adverse event and serious adverse event data collection through the open-label clinical study. Reporting of other events in addition to the Health Events of Interest will be available for participants not treated with tafamidis.

Shaded procedures are also performed in the primary THAOS study, and therefore need only be performed once per study visit.

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1. INTRODUCTION

Amyloidosis is a severely debilitating, and ultimately fatal, systemic condition induced by the accumulation of an insoluble fibrillar protein (amyloid) within tissues in amounts sufficient to impair normal function. Although there are more than 20 proteins that can form amyloid, the precursor protein transthyretin is associated with the most common familial amyloidosis, an autosomal dominant disease with variable clinical penetrance. Transthyretin (also referred to as pre-albumin), a 127-amino acid, 55 kDa protein that is primarily synthesized in the liver, is a transport protein of thyroxine and retinol-binding protein-retinol (vitamin A) complex (Blake 1978; Monaco 1995).[1, 5] Both natural sequence TTR and mutated variants of TTR are involved in amyloid disease but, a mutation in TTR accelerates the process of fibrillogenesis whereby the tetrameric structure of the TTR protein dissociates into monomers, and the folded monomers undergo partial denaturation to produce alternatively folded monomeric amyloidogenic intermediates. These intermediates then misassemble into soluble oligomers, profilaments, filaments, and amyloid fibril deposition (Hammarström 2002, Quintas 2001).[4, 6]

More than 100 TTR single site variants have been identified and associated with TTR amyloidosis (Connors, 2003).[2] The most common variant associated with polyneuropathy is V30M (valine replaced by methionine at position 30), accounting for approximately 85% of patients worldwide (Saraiva, 2001).[7] The overall worldwide population of patients with ATTR-PN is estimated at 5-10,000.

Tafamidis is a novel specific stabilizer of both tetrameric wild-type (w-t) TTR and of amyloidogenic variants of TTR. 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 TTR amyloidosis only, with no activity anticipated for other types of amyloidosis.

The Transthyretin –Associated Amyloidosis Outcomes Survey (THAOS) is a longitudinal, observational survey open to all patients with transthyretin-associated amyloidosis and participants with TTR mutations without a diagnosis of ATTR. 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-mutated TTR, and the genotypic-phenotypic relationship in ATTR. The principal aims of the outcome survey are to better understand and characterize the natural history of the disease by studying a large and heterogenous 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.

On 21 July 2011 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorization for the medicinal product tafamidis (Vyndaqel) 20 mg capsule intended for the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral

neurologic impairment. This granting of marketing authorization for Vyndaqel was made under exceptional circumstances. This study is a Post-Authorization Safety Study (PASS), in that it is a post-marketing commitment to the CHMP for Vyndaqel with the aim of providing longer term safety information relating to tafamidis.

1.1. Indication

Vyndaqel is indicated for the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment. This is the approved indication in the Summary of Product Characteristics for Vyndaqel (tafamidis) in the Committee for Medicinal Products for Human Use (CHMP) positive opinion.

1.2. Background and Rationale

1.2.1. Drug Development Rationale

Tafamidis binds to TTR at the thyroxine binding site and inhibits TTR tetramer dissociation, the rate limiting step in the production of the major neurototoxic early soluble aggregates and the ultimate formation of amyloid fibrils. By stabilizing the tetrameric native state of TTR, tafamidis increases the activation barrier associated with tetramer dissociation and therefore mimics the tetrameric stabilization effect observed with naturally occurring protective trans-suppressor variants. Tafamidis stops or slows the progression of disease and therefore represents a disease modifying therapy.

1.2.2. Study Rationale

The rationale for this THAOS substudy is based both on outcomes from completed clinical trials as well as the binding mechanism and stabilization characteristics of tafamidis.

Tafamidis has been shown to stabilize 36 of the 37 amyloidogenic variants tested thus far (with equivocal results obtained in one variant, believed to be related to the long storage conditions of the plasma sample). In addition, tafamidis stabilization is observed across the complete spectrum of variants, including those that are kinetically and/or thermodynamically less stable than wild-type TTR.

These stabilization rates *in vivo* have also be observed in patients. Stabilization rates in three clinical studies with patients with ATTR-PN taking tafamidis are shown in Table 1.

Table 1: Patients with TTR Stabilized by Study and Time Point (95% Confidence Intervals about Point Estimates for Percent Stabilized)

Month		Number Stabilized/Number Evaluated (%) and 95% CI							
		Study Fx-005			Study Fx-006		Fx1A-201 N=21	Fx1B-201	
		Tafamidis N=64	Placebo N=61	p-value	Placebo to Tafamidis N=41	Tafamidis to Tafamidis N=45		V122I N=4	Wild-Type N=31
Week 6 or Week 8	# Stabilized/ # Patients (%) 95% CI	62/63 (98.4) 95.3, 100	4/60 (6.7) 0.4, 13.0	<0.0001			18/19 (94.7) 74.0, 99.9	4/4 (100.0) 39.8, 100.0	30/31 (96.8) 83.3, 99.9
Month 6	# Stabilized/ # Patients (%) 95% CI	59/59 (100.0) 100, 100	3/58 (5.2) 0.0, 10.9	<0.0001			18/18 (100.0) 81.5, 100.0	3/4 (75.0) 19.4, 99.4	27/30 (90.0%) 73.5, 97.9
Month 12	# Stabilized/ # Patients (%) 95% CI	47/48 (97.9) 93.9, 100	1/50 (2.0) 0.0, 5.9	<0.0001			17/17 (100.0) 80.5, 100.0	3/4 (75.0) 19.4, 99.4	25/28 (89.3) 71.8, 97.7
Month 18	# Stabilized/ # Patients (%) 95% CI	47/48 (97.9) 93.9, 100	0/44 (0.0) 0.0, 0.0	<0.0001					
Month 19.5	# Stabilized /# Patients (%) 95% CI				35/37 (94.6) 81.8, 99.3	30/31 (96.8) 83.3, 99.9			
Month 24	# Stabilized/ # Patients (%) 95% CI				34/36 (94.4) 81.3, 99.3	31/32 (96.9) 83.8, 99.9			
Month 30	# Stabilized/ # Patients (%) 95% CI				32/34 (94.1) 80, 99	28/30 (93.3) 77, 99			

P-values for treatment comparability between placebo and tafamidis treatment for Study Fx-005 are based on a Chi-square test for proportions.

TTR stabilization rates for patients receiving tafamidis were similar among the four clinical studies, including Study Fx-006 placebo to tafamidis patients. TTR stabilization was over 92% (of patients) for each study at the first assessed time point (Week 6 for Studies Fx-006, Fx1A-201 and Fx1B-201 and Week 8 for Study Fx-005), demonstrating the rapid onset of stabilization following initiation of dosing. Further, stabilization at 12 months was observed in 97.9% of patients taking tafamidis in Study Fx-005, 91.4% of placebo to tafamidis patients in Study Fx-006, in 100% of patients in Study Fx1A-201, and in 87.5% of patients in Study Fx1B-201. These longer-term stabilization rates demonstrate the consistency and the persistence (ie, lack of tolerance) of TTR stabilization across 10 amyloidogenic variants and wild-type TTR.

Study Fx1A-201 was an open-label, multicenter, international study designed to determine TTR stabilization as well as tafamidis safety and tolerability, and its effects on clinical outcomes in 21 patients with non-V30M TTR amyloidosis. The duration of individual patient participation was approximately 14 months, including a 30-day screening period, 12 months of treatment, and a post-study follow-up contact 30 days after the last dose of study medication. Endpoints included the following:

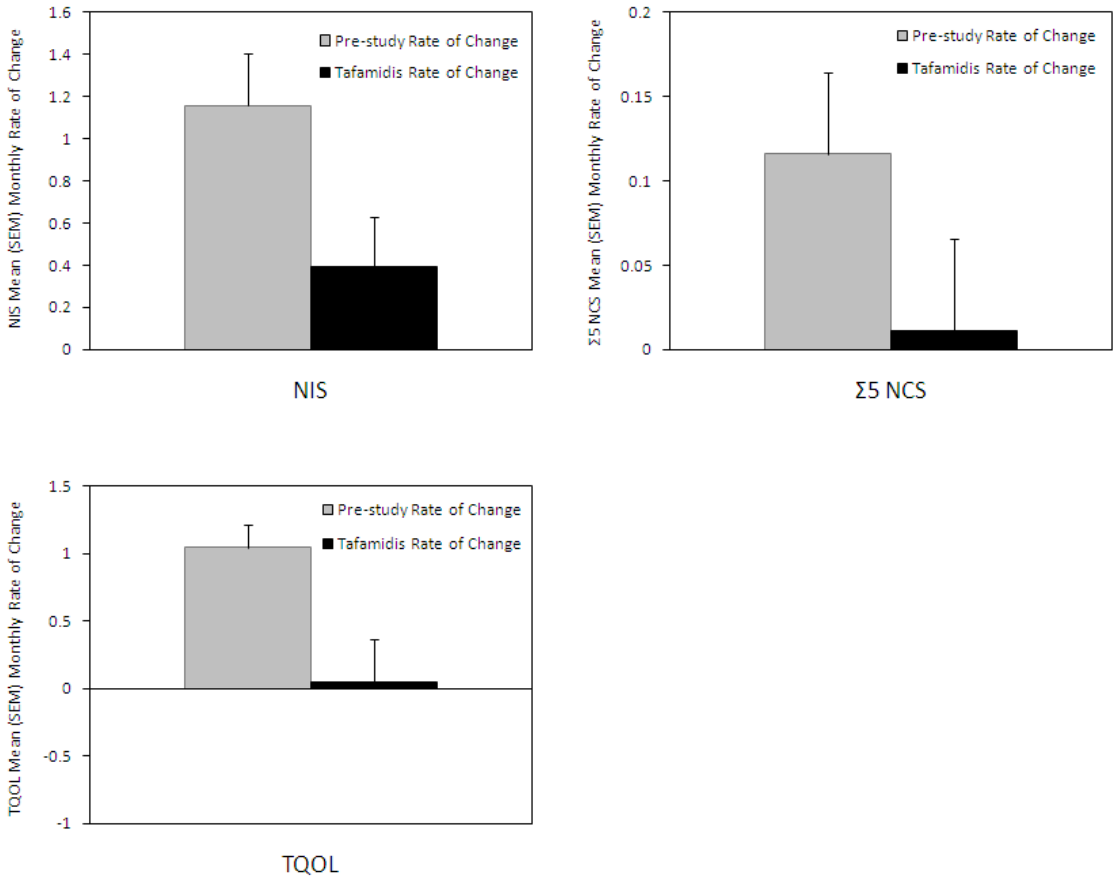
- Neuropathy Impairment Score (NIS). The NIS is a composite score assessing neurologic function that has been validated and utilized for registration trials in other neuropathies, including diabetic polyneuropathy (DPN). The NIS directly assesses muscle weakness and sensory loss, and unlike attributes of nerve conduction, is not a surrogate measure of such impairment but rather a direct measure. The NIS is the most commonly used instrument in trials assessing the efficacy of therapy in clinical neuropathy.

- Norfolk QOL-DN (TQOL score). The TQOL is a tool that was developed to capture patient-reported perceptions of neuropathy, particularly when the patient population is comprised of individuals with polyneuropathy as well as somatic and autonomic symptoms.

- Large nerve fiber function (Σ5 nerve composite score, NCS). Composite scores have been developed that enable the evaluation of small and large nerve fiber function. Composite endpoints reflecting nerve function in the lower limb have been found to be more sensitive in detecting abnormalities in patients with generalized peripheral neuropathy, particularly DPN and chronic idiopathic demyelinating polyneuropathy, compared with individual nerve conduction tests (Dyck, 2003; Dyck, 2005). NCS are objective and accepted measures of peripheral nerve fiber function that are sensitive to change. This specific large fiber function scale included five nerve conduction study attributes (sural nerve sensory nerve action potential; peroneal nerve compound muscle action potential, distal motor latency and velocity; and tibial nerve distal motor latency). The possible range of the Σ5 NCS nds is -15 to 15, with higher scores denoting worse large fiber neurologic function.

The monthly rate of change prior to the initiation of tafamidis treatment was estimated from the duration of symptoms prior to enrollment in Study Fx1A-201. This pre-study monthly rate of change was compared with the on-study monthly rate of change Outcomes from Study Fx1A-201 for these measures are provided in Figure 1.

Figure 1. Monthly Rates of Change in Efficacy Endpoints Prior to Enrollment (Pre-study) and During Treatment with Tafamidis – ITT Population (Study Fx1A-201)



There was a significantly slower rate of neurologic disease progression over the 12 months of tafamidis administration (NIS=0.39 units/month) when compared with the rate during the pre-study period (1.16 units/month, p=0.003). Note that, when expressed as an annual rate of change, the NIS increased 4.8 units/year, and was thus almost half that observed in the correlation study, where an average increase of 8.4 units/year was reported.

Study Fx-005 was a randomized (1:1), double-blind, placebo-controlled, multicenter, international study designed to evaluate the efficacy during 18 months of tafamidis 20 mg QD treatment in patients with early stage ATTR-PN, and specifically, to assess whether tafamidis impacted the rate of progression of the disease in patients diagnosed with ATTR-PN (and with a confirmed V30M mutation and positive amyloid biopsy).

The pivotal study of Vyndaqel was an 18-month, multicenter, randomized, double-blind, placebo-controlled study that evaluated the safety and efficacy of once-daily 20 mg tafamidis in 128 patients with TTR amyloid polyneuropathy with the V30M mutation and primarily stage 1 disease (do not routinely require assistance with ambulation). The primary outcome measures were the Neuropathy Impairment Score of the Lower Limb (NIS-LL – a physician

assessment of the neurologic exam of the lower limbs) and the Norfolk Quality of Life - Diabetic Neuropathy (Norfolk QOL-DN – a patient reported outcome, total quality of life score [TQOL]). Other outcome measures included composite scores of large nerve fiber (nerve conduction, vibration threshold and heart rate response to deep breathing - HRDB) and small nerve fiber function (heat pain and cooling threshold and HRDB) and nutritional assessments utilizing the modified body mass index (mBMI – BMI multiplied by serum albumin in g/L). Eighty-six of the 91 patients completing the 18 month treatment period subsequently enrolled in an open label extension study, where they all received once daily 20 mg tafamidis for an additional 12 months. Outcomes for the pre-specified analyses of the primary endpoints are provided in Table 2.

Table 2: Vyndaqel versus Placebo: NIS-LL and TQOL at Month 18 (Study Fx-005)

	Placebo	**Vyndaqel**
Pre-specified ITT Analysis	**N=61**	**N=64**
NIS-LL Responders (% Patients)	29.5%	45.3%
Difference (Vyndaqel minus Placebo)	15.8%	
95% CI of Difference (p-value)	-0.9%, 32.5% (0.068)	
TQOL Change from Baseline LSMean (SE)	7.2 (2.36)	2.0 (2.31)
Difference in LSMeans (SE)	-5.2 (3.31)	
95% CI of Difference (p-value)	-11.8, 1.3 (0.116)	
Pre-specified Efficacy Evaluable Analysis	**N=42**	**N=45**
NIS-LL Responders (% Patients)	38.1%	60.0%
Difference (Vyndaqel minus Placebo)	21.9%	
95% CI of Difference (p-value)	1.4%, 42.4% (0.041)	
TQOL Change from Baseline LSMean (SE)	8.9 (3.08)	0.1 (2.98)
Difference in LSMeans (SE)	-8.8 (4.32)	
95% CI of Difference (p-value)	-17.4, -0.2 (0.045)	

In the pre-specified ITT NIS-LL Responder analysis, patients who discontinued prior to the 18-month time point due to liver transplantation were categorized as non-responders. The pre-specified Efficacy Evaluable analysis used observed data for those patients who completed the 18 month treatment per protocol.

Because Study Fx-005 included primarily patients with the V30M genotype only, and did not include many patients with the non-V30M genotype, this current THAOS substudy is being performed to observe the effects of tafamidis in ATTR-PN patients with non-V30M genotype.

1.2.3. Safety Overview

The safety profile of tafamidis is based on exposure of 127 TTR amyloid polyneuropathy patients to 20 mg of tafamidis administered daily for an average of 538 days (range of 15 to 994 days). Note that of the 127 patients with ATTR-PN treated with tafamidis in the clinical development program, 21 (16.5%) had mutations other than V30M.

The population was adult patients diagnosed with symptomatic TTR amyloid polyneuropathy, with a mean age of approximately 44 years, approximately half of patients were female, and approximately 90% of patients were Caucasian. Adverse Drug Reactions (ADRs) were determined by including review of all treatment emergent adverse events, both serious and non-serious, regardless of investigator relatedness assessment, and review of vital

sign data, laboratory data (including electrocardiogram data) and discontinuations due to adverse events. In addition, other factors taken into consideration for the determination of ADRs included but were not limited to the mechanism of action of tafamidis, the known symptoms of the underlying TTR amyloidosis, the temporality of the adverse event to the administration of tafamidis, and the relative rates of comparative adverse events in the placebo groups in the controlled trials.

Based on the review of the totality of the available safety data, it was determined that there are four adverse events for which there is basis to believe there is a causal relationship between their occurrence and the use of tafamidis; as such these adverse events were identified as ADRs, with the incidence observed in the placebo-controlled 18 month Phase 2/3 Study Fx-005 presented in Table 3**.**

Table 3: Summary of Adverse Drug Reactions (Study Fx-005)

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

* Percentage based on the number of women (tafamidis n = 33; placebo, n = 37)

1.2.4. Dose Rationale

The dose for tafamidis is 20 mg once-daily.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

This non-interventional study will compare disease progression over at least 12 months of pre-treatment (patients will receive standard of care according to their treating physician) with disease progression over 12 months of tafamidis administration in symptomatic ATTR-PN patients with non-V30M mutations. Specific objectives are to:

- Quantify disease progression in the target population via at least a 12-month standard of care period.
- Evaluate the effects of 12 months of tafamidis therapy on disease progression following the 12-month standard of care period.
- Compare rates of disease progression before and after the initiation of treatment with tafamidis.

- Evaluate the safety of tafamidis in the study population.

Note that the duration of the standard of care period will be at least 1 year and may vary from patient to patient according to when commercial tafamidis becomes available in a particular country.

2.2. Endpoints

The primary objective of tafamidis therapy in this target population would be to slow or halt disease progression. This study will therefore utilize a series of neuropathy measures to assess disease progression and the effects of tafamidis treatment.

- Motor function (Medical Research Council scale).
- Sensory perception (pinprick, touch, vibration, position).
- Reflexes.
- Body mass index (BMI) and modified BMI (mBMI).
- Modified Polyneuropathy Disability (mPND) score.
- The safety and tolerability of tafamidis will be assessed via the collection of adverse events, including serious adverse events.

3. STUDY DESIGN

This is a substudy of the non-interventional THAOS survey. THAOS is a global, multi-center, longitudinal observational survey open to all patients with transthyretin-associated amyloidoses, including both inherited and wild-type disease, and participants with TTR mutations without a diagnosis of ATTR. It is open-ended with a minimum duration of 10 years. Patients will be followed as long as they are able to participate. THAOS is a non-interventional study and does not require the administration of an investigational agent or other intervention. The frequency and type of clinical and laboratory assessments will be performed according to the physician's standard of care. Physicians are not required to modify their standard assessments or treatment interventions for patients. Patients will continue to receive their current medications and all other standard care for their disease.

This substudy will enroll patients who are participants in the main THAOS protocol. THAOS sites that have enrolled ATTR-PN patients with mutations other than V30M will be contacted to participate; however, THAOS patients with symptomatic neuropathy with documented non-V30M mutation who are eligible to participate will be required to provide a separate written informed consent.

Once enrolled, patients will receive standard of care according to their treating physician and their rate of change in disease progression will be determined (as measured by the endpoints described in Section 7). Upon the commercial availability of tafamidis within each respective country, physicians will evaluate whether the patient is a candidate for tafamidis treatment as a commercial product. For those patients prescribed tafamidis 20 mg once-daily, the rate of change in disease progression will continue to be measured using the same endpoints, for 12 months. The rates of changes between the 2 periods (the standard of care period and then the tafamidis-treatment period) will be compared within-patient, and therefore patients will serve as their own control during this study. Due to the variable timing for commercial availability across countries, the duration of the standard-of-care period may be variable from patient to patient but is intended to be at least 1 year. Note that this sub-study is a Post-Authorization Safety Study (PASS) and is a post-marketing commitment to the CHMP for Vyndaqel-brand tafamidis. Treatment with commercially-available tafamidis will be according to the labeled indication.

Importantly, upon the commercial availability of tafamidis within each respective country, tafamidis 20 mg once-daily may be prescribed at the discretion of the Investigating physician to eligible patients. The patient is to return to the site to have a complete set of study assessments (motor function, sensory perception, etc.) completed prior to initiation of tafamidis treatment. Patients will then be followed for the next 12 months per the study protocol.

Consented non-V30M patients will undergo the following assessments upon sub-study entry at baseline and at least annually and preferably every 6 months: demographics, ATTR-PN-related symptoms, vital signs, clinical laboratory testing, echocardiography, a full neurological examination (including motor function as assessed on the MRC scale, sensory perception to pinprick, touch, vibration, and position, and reflexes), mPND (a walking disability scale), EQ5D, Norfolk QOL-DN, BMI, and adverse event collection.

3.1. Liver transplant

There may be patients who, following enrollment into this substudy, become eligible for liver transplant. If these patients elect to have a transplant, they will be continued in THAOS but will NOT be eligible for tafamidis treatment and will be discontinued from this substudy.

4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject. Note that all subjects enrolled should meet the usual prescribing criteria for tafamidis as per the local product information and should be entered into the study at the investigator's discretion.

4.1. Inclusion Criteria

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

1. Patient has symptomatic peripheral and/or autonomic neuropathy with documented non-V30M mutation (excluding V122I and L111M). If the patient has not yet had genotype confirmation, this must be performed prior to enrollment.

2. Must be able to be a participant in the THAOS registry and are either currently enrolled and will be enrolled in THAOS at the same time as entry into this study.

3. Patient provides written informed consent to participate in this sub-study. Patient must have already provided written informed consent to participate in the THAOS registry.

4. If female, and should the patient receive commercial tafamidis, the patient is post-menopausal or willing to use birth control during the study and for 1 month after discontinuing study medication.

5. Patient is, in the opinion of the Investigator, willing and able to comply with the study activities. Performance of procedures as recommended will promote a consistent data set and should be consistent with the patient's needs and the local standard of care. At enrollment, protocol-specified procedures should be consistent with the patient's clinical needs.

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

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

- Subjects who are willing and able to comply with scheduled visits, the substudy treatment plan, laboratory tests, and other substudy procedures.

4.2. Exclusion Criteria

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

1. Participant has a diagnosis of primary or secondary amyloidosis.

2. If female, participant is pregnant, as assessed by urine pregnancy test.

3. Subjects who are investigational site staff members or subjects who are Pfizer employees directly involved in the conduct of the trial.

4. Patient has documented V30M, V122I, or L111M mutation.

5. Patient has received a liver transplant.

6. Patient has an mPND score of ≥3 (requires assistance with ambulation).

7. Patient does not have symptomatic ATTR-PN.

8. Patient has received treatment with tafamidis prior to entry into this sub-study.

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

10. Patient received an investigational drug/device in another clinical investigational study within 60 days before Baseline (Day 0).

11. Patient had active alcohol or substance abuse within 60 days before Baseline (Day 0).

12. Patient has a history of documented noncompliance.

13. Participation in other studies (other than the THAOS survey) that include medication treatment within 6 months before the current study begins and/or during study participation.

14. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

Patients will be enrolled into the study based on the results of presumptive TTR genotyping conducted by the investigational site. If the investigational site does not have genotyping capabilities, the reference laboratory may be utilized to establish the diagnosis. At the time of baseline examination, a patient buccal swab will also be obtained at the investigational site for shipment to a reference laboratory for confirmation of the genotype result obtained by the site.

If the reference laboratory does not confirm the genotype result reported by the site, a re-test will be performed by the reference laboratory. Patients who are confirmed as false positives will be dropped from the study and will be replaced.

4.3. Randomization Criteria

This is a non-interventional, open-label, single-sequence study in which each patient will have at least a 12-month standard of care period (or until commercial tafamidis is available in their country) and then, at the discretion of the physician, may be treated with 12 months of commercial tafamidis. Thus, no randomization is required for this study.

4.4. Life Style Guidelines

Should the patient be prescribed tafamidis by the PI, female patients must be surgically sterile or be postmenopausal, or must agree to use effective contraception during the tafamidis treatment and for at least 30 days after discontinuation of treatment (if applicable). The decision of effective contraception will be based on the judgment of the principal investigator or a designated associate.

5. STUDY TREATMENTS

During the first period of this study there is no study treatment defined; patients will receive standard of care according to their treating physician. Following commercial availability of tafamidis in their country, and at the discretion of the PI, patients may be prescribed commercial tafamidis 20 mg once-daily and followed for 12 months.

Tafamidis meglumine [N-methyl D-(2,3,4,5,6-pentahydroxy-hexyl)-ammonium; 2-(3,5-dichloro-phenyl)-benzoxazole-6-carboxylate] is the meglumine salt of 2-(3,5-dichloro-phenyl)-benzoxazole-6-carboxylic acid (Fx-1006).

5.1. Allocation to Treatment

This is a single-sequence study in which all patients may receive the same treatment. Upon the commercial availability of tafamidis within each respective country, and at the discretion of the PI, tafamidis 20 mg once-daily will be prescribed by the investigating physician to eligible patients. The patient should return to the site to have a complete set of study assessments (motor function, sensory perception, etc.) performed prior to initiation of tafamidis treatment. The patient will then be followed for the next 12 months per the study protocol.

5.2. Breaking the Blind

This is an open-label study and therefore there will be no blind. Patients and investigators will be aware of the treatment given.

5.3. Drug Supplies

Commercially-available tafamidis is to be provided to the patients as prescribed by their physician. The investigator should review the package insert prior to prescribing tafamidis.

The use and dosage recommendations for tafamidis will take place on the basis of the approved Product Label/SmPC and will be adjusted solely according to medical and therapeutic necessity.

5.4. Concomitant Medication(s)

Concomitant medications are allowed per the standard of care, except for non-sub-study allowed NSAID. The following NSAIDs are allowed: acetylsalicylic acid, etodolac, ibuprofen, indomethicin, ketoprofen, nabumetone, naproxen, nimesulide, piroxicam, and sulindac. Commercial tafamidis will be prescribed by the physician and the package insert should be referred to for information regarding the use of concomitant medications.

Concomitant medication class will be collected; however, if a concomitant medication is given in response to an adverse event, the full mediation data (including class and term as well as start dates and dose) should be recorded on the data capture forms.

6. STUDY PROCEDURES

This study will have 3 periods: screening, standard of care, and commercial tafamidis treatment. The following sections provide details as to the assessments to be performed within each period at each study visit. Note that screening procedures can be performed in a single visit as the Day 0 assessment, or can be performed during two separate visits.

6.1. Screening/Day 0

Screening evaluations may be performed to determine patient eligibility for the study. Screening evaluations may include:

- Informed consent, to be completed prior to the patient engaging in any study procedure or assessment.
- Eligibility review (confirmation of suitability for participation based on inclusion and exclusion criteria).
- Genotype testing for confirmation of the appropriate mutation(s) for study entry.
- Medical history.
- General examination (including height and weight for body mass index, vital signs, Karnofsky Performance Index).
- Serum albumin (for mBMI), liver function tests, thyroid function tests, and transthyretin levels.
- Urine test for pregnancy (for women of childbearing potential).
- Motor function (Medical Research Council Scale).
- Sensory Perception (pinprick, touch, vibration, position).
- Reflexes.

- Norfolk QOL-DN.
- EQ-5D.
- Modified Polyneuropathy Disability (mPND).
- 12-lead ECG and echocardiogram.
- Concomitant medications.

Screening laboratory tests can be completed on the baseline day (Day 0). Before engaging in any study procedure, each patient must sign and date an informed consent form. The date the informed consent form is signed must be documented in the patient's eCRF.

6.2. Pre-Treatment Period

Patients who are determined eligible for the study based on the Screening evaluations may return to the study center every 6 months. At these visits, the following procedures may be performed:

- General examination (including height and weight for body mass index, vital signs, Karnofsky Performance Index).
- Serum albumin (for mBMI), liver function tests, thyroid function tests, and transthyretin levels.
- Urine test for pregnancy (for women of childbearing potential).
- Motor function (Medical Research Council Scale).
- Sensory Perception (pinprick, touch, vibration, position).
- Reflexes.
- Norfolk QOL-DN.
- EQ-5D.
- Modified Polyneuropathy Disability (mPND).
- ECG and echocardiography
- Review of Health Events of Interest.
- Review concomitant medications

6.3. Initiation of Tafamidis Treatment Period

Upon commercial availability of tafamidis in the resident country of each patient, but prior to the patient being prescribed tafamidis therapy, the patient may return to the clinic for the following procedures:

- Review of Eligibility Criteria and Start Date of Tafamidis Therapy.
- General examination (including height and weight for body mass index, vital signs, Karnofsky Performance Index).
- Serum albumin (for mBMI), liver function tests, thyroid function tests, and transthyretin levels.
- Urine test for pregnancy (for women of childbearing potential).
- Motor function (Medical Research Council Scale).
- Sensory Perception (pinprick, touch, vibration, position).
- Reflexes.
- Norfolk QOL-DN.
- EQ-5D.
- Modified Polyneuropathy Disability (mPND).
- Review concomitant medications
- ECG and echocardiography.
- Review of Health Events of Interest.

Upon completion of this visit, the patient may, at the physician's discretion, be prescribed tafamidis and instructed to take the medication according to the package insert.

6.4. Tafamidis Treatment Period (Month 6 of Tafamidis Treatment)

Patients may return to the study center at the 6 months time point following initiation of tafamidis. At this visit, the following procedures may be performed:

- General examination (including height and weight for body mass index, vital signs, Karnofsky Performance Index).
- Serum albumin (for mBMI), liver function tests, thyroid function tests, and transthyretin levels.

- Urine test for pregnancy (for women of childbearing potential).
- Motor function (Medical Research Council Scale).
- Sensory Perception (pinprick, touch, vibration, position).
- Reflexes.
- Norfolk QOL-DN.
- EQ-5D.
- Modified Polyneuropathy Disability (mPND).
- ECG and echocardiography.
- Review of adverse events and Health Events of Interest.
- Review concomitant medications

6.5. Final Study Visit (Month 12 of Tafamidis Treatment)

Upon the completion of 12 months of tafamidis therapy, patients may return to the site for a final study visit. At this visit, the following procedures may be performed:

- General examination (including height and weight for body mass index, vital signs, Karnofsky Performance Index).
- Serum albumin (for mBMI), liver function tests, thyroid function tests, and transthyretin levels.
- Urine test for pregnancy (for women of childbearing potential).
- Motor function (Medical Research Council Scale).
- Sensory Perception (pinprick, touch, vibration, position).
- Reflexes.
- Norfolk QOL-DN.
- EQ-5D.
- Modified Polyneuropathy Disability (mPND).
- ECGs and ECHOs.

- Review of adverse events and Health Events of Interest.
- Review concomitant medications
- End of Study form, including date of last dose of tafamidis during the study period, and whether or not the patient will be continuing tafamidis after completion of the study.

This will be the final study visit for this sub-study. Participation in the main THAOS protocol will continue per that protocol.

6.6. Subject Withdrawal

Subjects may withdraw from the substudy 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. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible, on the End of Study Form. The investigator should inquire about the reason for withdrawal, and request the subject to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved serious adverse events.

If a patient withdraws consent, every effort should be made to have the patient complete the end-of-study assessments. If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

There may be patients who, following enrollment into this substudy, become eligible for liver transplant. If these patients elect to have a transplant, they will be continued in THAOS but will NOT be eligible for tafamidis treatment and will be discontinued from this substudy.

7. ASSESSMENTS

7.1. Efficacy Assessments

This study will utilize a series of neuropathy measures to assess disease progression and the effects of tafamidis treatment.

- Motor function (Medical Research Council scale).
- Sensory perception (pinprick, touch, vibration, position).
- Reflexes.
- Body mass index (BMI) and modified BMI (mBMI).
- Modified Polyneuropathy Disability (mPND) score.

- Norfolk Quality of Life – Diabetic Neuropathy (Norfolk QOL-DN).
- EuroQoL – 5 Dimensions (EQ-5D).

These assessments are described in the following sections.

7.1.1. Motor Function (Medical Research Council Scale)

Motor function will be assessed by the MRC scale. The MRC has a scale of 0 (no contractions) to 5 (full range of motion); total score range 0 to 160 and is derived from the standard neurological motor examination.

7.1.2. Sensory Perception (Pinprick, Touch, Vibration, Position)

Sensory perception will be scored as normal (0), decreased (1), and absent (2); total score range 0 to 128 and is derived from the standard neurological sensory examination.

- Pinprick (0 [normal] to 44 [insensate]);
- Light touch (0 [normal] to 44 [insensate]);
- Vibration (0 [normal] to 24 [insensate]);
- Position (0 [normal] to 16 [insensate]).

7.1.3. Reflexes

Reflexes will be scored as present (0) and absent (1); total score range 0 (normal) to 10 (areflexic) and are derived from the standard neurological reflex examination.

7.1.4. Body Mass Index (BMI) and Modified BMI (mBMI)

The use of a modified body mass index (mBMI), as compared to the standard BMI measure, compensates for the edema formation associated with ATTR-PN, in which patients may experience swelling and thus increased weight associated with their malnutrition (resulting from the gastrointestinal disturbances of ATTR-PN). Modified BMI also correlates closely with survival in ATTR-PN patients who have not received liver transplant. Thus the mBMI provides a more accurate measure of body mass index in the subject population than the classic BMI measure. Each participant's height, weight, and serum albumin will be collected at each specified visit in order for the mBMI to be derived.

Investigational centers will not be required to derive the mBMI [this will be calculated during the statistical analysis by multiplying the BMI (kg/m^2) by serum albumin level (g/L)].

7.1.5. Modified Polyneuropathy Disability (mPND) Score

Peripheral sensory and motor disturbances will be assessed by the mPND (see Sharma 2003) (also referred to as the walking disability score in the THAOS data screens) are scored as follows:

- Score 1: sensory disturbances in the limbs without motor impairment.
- Score 2: difficulty walking without the need of a walking aid.
- Score 3a: one cane or crutch required for walking.
- Score 3b: two canes or two crutches needed.
- Score 4: wheelchair required or patient confined to bed.

7.1.6. Norfolk QOL-DN

Quality of Life (QOL) will be assessed using the Norfolk QOL-DN, a tool which was developed to capture patient-reported aspects of neuropathy, particularly when the patient base is comprised of subjects with polyneuropathy and somatic and autonomic symptoms. The Norfolk QOL-DN has been used to evaluate several diabetic neuropathy drugs in clinical trials. The developers showed in a study population in Germany with five stages of neuropathy severity according to the criteria of Dyck et al (Dyck 1993)[3] that Norfolk QOL-DN was able to discriminate the presence of neuropathy and distinguish the stages within the population (Vinik 2004).[9]

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

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

The primary measure from the Norfolk QOL-DN will be the TQOL.

See Appendix 1 for a sample of the Norfolk QOL-DN as well as a description of how to administer and score the scale. The Norfolk QOL-DN is collected at each visit in the THAOS registry.

7.1.7. EuroQoL – 5 Dimensions (EQ-5D)

The EQ-5D is collected at each visit in the THAOS registry. The EQ-5D is a 100-point scale that allows a subject to describe his/her health state 'today', rating from 'Worst imaginable health state' (score of 0) to 'Best imaginable health state' (score of 100).

7.2. Safety Assessments

7.2.1. Adverse Events

Adverse events will be collected during both the standard of care period and the tafamidis-treatment period. Adverse event and serious adverse event 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 4, corresponding data for Health Events of Interest will be collected to characterize both the natural history of TTR amyloidoses in participants not treated with tafamidis and safety concerns amongst tafamidis-treated participants.

Table 4. Summary of Ongoing Safety Concerns to be Assessed in THAOS

Important identified risks (Adverse Drug Reactions)	Urinary tract infection Diarrhea Vaginal infections Upper abdominal pain
Important potential risks	Hepatotoxicity Hypersensitivity reactions Reproductive toxicity Thyroid dysfunction particularly in pregnant women
Important missing information	Safety and efficacy in elderly patients Longer term effects on survival and safety

An adverse event is defined as any untoward medical occurrence in a patient administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An adverse event could be any unfavorable and unintended sign (eg, including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study medication, whether or not it is considered study medication related. This includes any newly occurring event or previous condition that had increased in severity or frequency since the administration of study medication. See Section 8 for detail on adverse event reporting.

7.2.2. Vital Signs

Vital signs measured should include systolic and diastolic blood pressure (mmHg) and pulse (beats per minute), both lying and standing, oral temperature (°C), and respiration rate (breaths/minute).

Every effort should be made to ensure that the protocol tests and procedures are completed as described. However it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, where it may not be feasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well being of the subject.

7.2.3. Clinical Laboratories

Serum albumin (for mBMI), thyroid function tests, and transthyretin levels may be collected at each study visit. In addition, liver function tests may be collected, as follows:

- Total bilirubin.
- Direct bilirubin.
- Alkaline phosphatase.
- Aspartate transaminase (AST).
- Alanine transaminase (ALT).
- Gamma-glutamyl transferase (GGT).

7.2.4. Echocardiograms and Electrocardiograms

Echocardiograms and electrocardiograms will be performed upon entry to the study and annually thereafter. Further, ECHO and ECG should be performed at the initiation of the tafamidis treatment period and at the end of the study (or upon early termination).

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered adverse events regardless of treatment group (if applicable) or suspected causal relationship to tafamidis will be recorded on the adverse event page(s) of the case report form (CRF) as follows.

For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event (see section "Serious Adverse Events") requiring immediate notification to Pfizer or a Pfizer-designated representative. For all adverse events,

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

8.2. Reporting Period

For serious adverse events, the reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent or signed data privacy statement, which is obtained prior to the subject's participation in the study through and including 28 calendar days after the last administration of the study drug within the observational period.

8.3. Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease.

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

- Drug overdose;
- Drug withdrawal;
- Drug abuse;
- Drug misuse;
- Drug interactions;
- Drug dependency;
- Extravasation;

- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error.

8.4. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event 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 adverse event by the investigator or sponsor.

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

8.5. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Results in congenital anomaly/birth defect.

Lack of efficacy should be reported as an adverse event when it is associated with a serious adverse event.

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 adverse event outcomes, the important medical event should be reported as serious.

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

8.6. Hospitalization

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

Hospitalization in the absence of a medical AE is not in itself an AE and is not to be reported. 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 worsening of a 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).

8.7. Causality Assessment

The investigator's assessment of causality must be provided for all adverse events (serious and non-serious). The investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that tafamidis caused or contributed to an adverse event. If the investigator's final determination of causality is unknown and the investigator does not know whether tafamidis caused the event, then the event will be handled as related to tafamidis for reporting purposes. If the investigator's causality assessment is unknown but not related to tafamidis this should be clearly documented in the CRF.

8.8. Exposure During Pregnancy

An exposure during pregnancy (also referred to as exposure in-utero [EIU]) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or 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. A male has been exposed, either due to treatment or environmental, to tafamidis prior to or around the time of conception and/or is exposed during his partner's pregnancy (paternal exposure).

If any study subject or study subject's partner becomes, or is found to be, pregnant during or within 1 month of discontinuation of the study subject's treatment with tafamidis, the investigator must submit this information to Pfizer within 24 hours of awareness of the pregnancy, irrespective of whether an adverse event has occurred, and through the Tafamidis Enhanced Surveillance for Pregnancy Outcomes (TESPO) program. Reporting to TESPO will also include a 12-month post-birth followup questionnaire regarding developmental milestones.

Follow-up is conducted to obtain pregnancy outcome information on all Exposure in Utero reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination (eg, induced abortion) and then notify Pfizer of the outcome. The investigator will provide this information as a follow up to the initial EIU report.

8.9. Medication Error

A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is 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 whether an adverse event occurred:

- 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;

    - A medication error including potential medication error or near miss.

8.10. Reporting Requirements

Each adverse event is to be assessed to determine if it meets the criteria for serious adverse events.

If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate.

8.11. Serious Adverse Event Reporting Requirements

If a serious adverse event occurs, Pfizer is to be notified within 24 hours of awareness of the event by the investigator. In particular, if the serious adverse event is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports as well as to the initial and follow-up reporting of exposure during pregnancy, exposure during breast feeding and medication error cases.

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

For all serious adverse events, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for serious adverse events is more detailed than that captured on the adverse event case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.12. Communication of Issues

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

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

9. DATA ANALYSIS/STATISTICAL METHODS

This study is designed to assess the within-patient rates of change for key neuropathy measures that assess ATTR-PN disease progression. The analysis methods planned are consistent with that objective. A detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan, which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

As this study will include annual interim reporting, the status of patients in each period (whether in the standard of care period or the tafamidis treatment period) will be presented; select tabulations will be provided overall as well as by country. All data captured on the case report form will be included in data listings.

9.1. Sample Size Determination

There are limited patients with non-V30M ATTR-PN. Thus, powering a study to detect statistical differences is not feasible. However, difference in slopes for outcome parameters, eg, for the motor function (assessed by the MRC scale), between the standard of care period and the tafamidis treatment period can be measured in the context of this substudy that will provide precise numerical estimates of the effects of tafamidis treatment following a period of standard of care. Given the number of non-V30M patients anticipated to be enrolled in the THAOS registry who would qualify for treatment with tafamidis per the product label, a sample size of approximately 50 patients could be enrolled into this study. With an assumption of 52 patients enrolled, this study will have over 80% power (with alpha of 0.05) to detect an effect size of 0.4 using a two-sided one-sample (paired) t-test.

9.2. Baseline Characteristics and Patient Disposition

Demographic and baseline characteristics will be tabulated. Patient disposition and reasons for early termination will be tabulated.

9.3. Efficacy Analysis

Conclusions regarding the effects of tafamidis will be made based on a preponderance of evidence, including consistency and directionality, across all the endpoints, including motor function and sensory perception (pinprick, touch, vibration, position), as well as reflexes and other measures. Therefore, no single efficacy endpoint will be designated as primary.

9.3.1. Analysis of Primary Endpoint

Descriptive statistics will be provided for each period (the standard of care period and the tafamidis treatment period) for each neuropathy endpoint.

The rate of disease progression per month (as measured by the slope of the change from the start of each period to the end of each period) will be determined for each patient for each endpoint. The rates of disease progression between the standard of care period and the tafamidis treatment period will then be compared via a 2-sided paired t-test. Thus, each patient will act as his/her own control for each analysis.

In addition to assessment of each endpoint on its own, determination of the association between endpoints (and their changes over time) will be performed. Plots of the time course of each endpoint will be provided. The number (and percent) of patients having a slower rate of progression during the tafamidis period (than for the standard of care period) will be derived for each endpoint.

9.3.2. Analysis of Secondary Endpoints

As this study is intended to enrich the knowledge base regarding disease progression of non-V30M ATTR-PN patients under the current standard of care as well as to provide data regarding the effects of tafamidis on disease progression, additional exploratory analyses (beyond those described here) may be performed. For instance, assessment of each individual motor component item from the MRC scale may be performed to better describe the nature of the distal-to-proximal changes in disease over time.

9.4. Safety Analysis

9.4.1. Adverse Events

All AEs will be classified using MedDRA and presented by system organ class and preferred term (higher level terms were listed only). All summaries will included the number and percentage of patients reporting each event.

Serious adverse events will be tabulated and a narrative will be written for each patient experiencing a serious adverse event. Similarly, AEs resulting in discontinuation of study medication will be will be tabulated and a narrative will be written for each patient accordingly. Health Events of Interest will also be summarized before and after tafamidis treatment.

9.4.2. Vital Signs

Systolic and diastolic blood pressure and pulse (supine and standing), oral temperature, and respiratory rate measures will be listed by treatment, patient, and date.

9.5. Interim Analysis

Data collected during this study will be regularly reviewed by the Sponsor. A report that will include a full set of tables, listings, and figures will be prepared annually. Those interim reports will adhere to the analysis as described above where data allow (for instance, during the first year of the study there may be insufficient patients who have progressed to the tafamidis treatment period to allow for derivation of rates of change during that period). This is an open-label study and data will be regularly reviewed; there will be no adjustment of overall alpha due to these data reviews.

9.6. External Scientific Steering Committee

This study will utilize an External Scientific Steering Committee.

9.7. Liver Transplant Patients

There may be patients who, following enrollment into this substudy, become eligible for liver transplant. If these patients elect to have a transplant, they will be continued in THAOS but will NOT be eligible for tafamidis treatment and will be discontinued from this substudy.

10. QUALITY CONTROL AND QUALITY ASSURANCE

The study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Ccommittee (IEC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term Case Report Form (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 database, allowing sites to enter data remotely through locally secured connections. The computer based application and the data to be collected and entered are included in the THAOS User's Manual, which will be provided to each site.

Pre-printed THAOS worksheets will be provided to survey sites to aid in the accurate recording and collection of data for each patient visit. Data should be entered as soon as feasible after the patient's assessment is completed.

Prior to initiating the survey, the Sponsor or its designee will train the THAOS physician and site staff to use the database and review the User's Manual. Ongoing technical support will be provided to survey sites by a database development company.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to ICH, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

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

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, 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 in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

12.2. 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 such as *Good Pharmacoepidemiology Practices* (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidances, Pharmaceutical Research and Manufacturers Association (PhRMA) guidelines and similar.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data.

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

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

The investigator must ensure that each study subject, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent form.

12.4. Subject Recruitment

All patients will be enrolled from the THAOS registry. No recruitment (eg, advertising) by investigators will be performed for this study.

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

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

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

13. PUBLICATION OF STUDY RESULTS

Publication of study results is discussed in the Clinical Study Agreement.

13.1. Communication of results by Pfizer

Pfizer fulfils its commitment to publicly disclose the results of studies through posting the results of this study on ClinicalStudyResults.org. Pfizer posts the results of studies that fall into either of the following categories:

- Studies that Pfizer registered on www.clincaltrials.gov regardless of the reason for registration; OR

- All other studies for which the results have scientific or medical importance as determined by Pfizer.

Results are posted in two formats:

- The results of studies applicable under the US Food and Drug Administration Amendments Act of 2007 (FDAAA) and/or An Act Regarding Advertising by Drug Manufacturers and Disclosure of Clinical Trials (state of Maine Reporting Requirements) are posted on ClinicalTrials.gov in a tabular format called Basic Results.

- The results of all required studies (even if not previously registered to ClinicalTrials.gov) and any voluntarily registered studies are posted on ClinicalStudyResults.org in a format called a Pharmaceutical Research and Manufacturers of America (PhRMA) website synopsis (PWS), the format established by the ICH-E3 Clinical Study Report (CSR) Synopsis.

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

- For studies involving products already approved in any country and applicable under FDAAA and/or state of Maine, Pfizer posts results within one year of the primary outcome completion date (PCD). For all other studies that do not involve a Pfizer product, Pfizer posts results one year from last, subject last visit (LSLV);

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

- For studies involving products whose drug development is discontinued before approval, Pfizer posts the results within one year after such discontinuation.

Primary Completion Date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.

Pfizer posts citations only for publications that are accessible in recognized (searchable) publication databases. Single-centre results publications for a multi-centre study are generally not posted because they may not accurately reflect the results of the study.

13.2. Publications by Investigators

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

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

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

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

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

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

14. REFERENCES (ALPHABETICAL ORDER)

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Appendix 1. Norfolk Quality of life – Diabetic Neuropathy

Part I: Symptoms

Have you had any of the following symptoms in the past 4 weeks? Please Check all that apply.

	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?	❑	❑	❑	❑	❑

In the past 4 weeks, how much difficulty have you had performing the following activities:

22. Bathing/Showering?	❑	❑	❑	❑	❑
23. Dressing?	❑	❑	❑	❑	❑
24. Walking?	❑	❑	❑	❑	❑
25. Getting on or off the toilet?	❑	❑	❑	❑	❑
26. Using eating utensils?	❑	❑	❑	❑	❑

Answer these questions according to the following scale:	Not at all **0**	A little **1**	Somewhat **2**	Moderately **3**	Severely **4**
In the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical or emotional health?					
27. Cut down on the amount of time you spent on work or other activities?	❑	❑	❑	❑	❑
28. Accomplished less than you would like?	❑	❑	❑	❑	❑
29. Were limited in the kind of work or other activities you could perform?	❑	❑	❑	❑	❑
30. Had difficulty performing the work/other activities (it took extra effort)?	❑	❑	❑	❑	❑

31. In general, would you say your health now is:

Excellent	Very Good	Good	Fair	Poor
❑	❑	❑	❑	❑

32. Compared with 3 months ago, how would you rate your health in general now?

Much Better	Somewhat Better	About the Same	Somewhat Worse	Much Worse
❑	❑	❑	❑	❑

Answer these questions according to the following scale:	Not at all **0**	A little **1**	Somewhat **2**	Moderately **3**	Severely **4**
33. In the past 4 weeks, to what extent has your physical health interfered with your normal social activities with family, friends, neighbors, or groups?	❑	❑	❑	❑	❑
34. In the past 4 weeks, how much did **pain** interfere with your normal work (including work both outside the home and housework)?	❑	❑	❑	❑	❑
35. In the past 4 weeks, how much did **weakness or shakiness** interfere with your normal work (including work both outside the home and housework)?	❑	❑	❑	❑	❑

Manual and Scoring Algorithm for QOL-DN

1.) Description:

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

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

These scales and the administration of the questionnaire are described in detail below. In general, items 1-7 (Part I) are a simple inventory of symptoms of neuropathy. The presence of the symptom is checked in whichever box applies, and an absence of a symptom is checked under "none." Positive responses are scored as 1; and negative responses, as 0. Items 8-35 (Part II) pertain to Activities of Daily Life, and most of these are scaled on a 5-point Likert scale ranging from 0 ("Not a problem") to 4 ("Severe problem"). However, Question 32 is the only one scored differently. "About the Same" (the middle item) is scored as 0. "Somewhat better" is scored as -1. "Much better" is scored as -2. "Somewhat worse" is scored as 1, and "Much worse" is scored as 2.

A final important point of the overall instrument is that the patient/subject is instructed to rate most items **over the last 4 weeks**, so responses should be interpreted as cumulative over that time period - not merely an inventory of the patient's status at the moment of filling out the questionnaire.

2.) Administering the questionnaire:

Administering the questionnaire to the patient or experimental subject is very straightforward: the patient simply fills out the paper form. It is important that the patient is in a quiet area, free of undue distractions, and patients are encouraged to answer the questions themselves (ie, spouses and significant others should not fill out the questionnaire or influence the patient's responses). *These are subjective patient responses.* The responses are coded and scored when they are entered into the appropriate database, and the algorithm is supplied below. All questions should be answered. The gender-specific sexual functions

questions located on the biographical page should obviously be answered according to gender. It is not recommended to compare responses on this questionnaire directly to the patient's medical history or any other sources of similar information such as other pain questionnaires, etc.

3.) Sub-scales and Scoring Algorithm:

The scales listed above were determined based on an exploratory factor analysis, so the questions have loaded into their respective domains. All symptoms (1-7) are scored as either a 1 or a 0, indicating a presence or absence of the symptom. With the exception of Question 32, the other items are scored according to the 5-point Likert Scale (0-4, "No Problem" to "Severe Problem"). Question 32 is scored as follows: -2, "Much Better"; -1, "Somewhat Better"; 0 "About the Same"; 1, "Somewhat Worse"; and 2, "Much Worse."

The Total QOL and five domains should be summed as follows:

- Total QOL Σ(1-7, 8-35)
- Physical Functioning/Large Fiber Σ(8, 11, 13-15, 24, 27-35)
- Activities of Daily Living (ADLs) Σ(12, 22, 23, 25, 26)
- Symptoms Σ(1-7, 9)
- Small Fiber Σ(10, 16, 17, 18)
- Autonomic Σ(19, 20, 21)

These scales and subscales are calculated without weighting of any kind, and reported as the integer sum of the listed questionnaire items.

Appendix 2. EQ-5D

THAOS Transthyretin Hereditary Amyloidosis Outcomes Survey

Patient Assessments

Patient no.: ☐☐☐☐☐☐☐ Patient Initials:: ☐☐☐

VISIT: ☐ Date of Visit: ☐☐/☐☐☐/☐☐☐☐

EQ-5D HEALTH QUESTIONNAIRE (Page 1 of 2)

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 ☐

THAOS Transthyretin Hereditary Amyloidosis Outcomes Survey
Patient Assessments

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

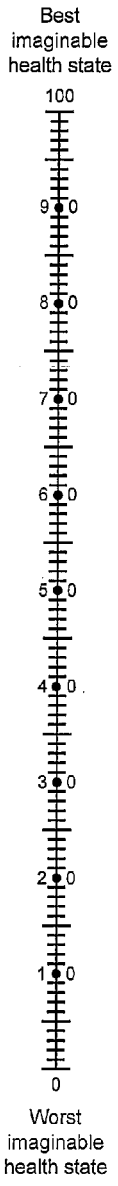
VISIT: | Date of Visit: | | / | | | / | | | |

EQ-5D HEALTH QUESTIONNAIRE (Page 2 of 2)

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



Appendix 3. Modified Polyneuropathy Disability Score (mPND)

Score	Definition
0	Normal
1	Sensory disturbances in limbs without motor impairment
2	Difficulty walking without the need of a walking aid
3a	One cane or one crutch required for walking
3b	Two canes or two crutches needed
4	Wheelchair required or patient confined to bed