NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	**T**afamidis 61mg, **Outcomes** in ATTR **A**myloidosis with Neurologic and **M**ultisystemic Involvement - TRAMA
Protocol number	B3461104
Protocol version identifier	1.0
Date	17 February 2022
Active substance	Tafamidis free acid 61 mg
Hypotheses and Objectives	**Hypotheses and Objectives**: Tafamidis free acid 61 mg has been shown (compared to placebo) to reduce the combination of all-cause mortality and the frequency of cardiovascular (CV) related hospitalizations, as well as to slow the decline in functional capacity and quality of life (QoL) of patients with ATTR-CM of hereditary (v) or wild-type (wt) origin. In this study the hypothesis is that tafamidis free acid 61 mg reduces the progression of neurological variables in ATTRv and ATTRwt patients with neurologic involvement. The objective of the study is to conduct a retrospective study to evaluate the efficacy of tafamidis 61 mg on non-cardiac variables in patients with ATTRv and ATTRwt, included in the ATTR-ACT (B3461028) and/or LTE (extension study) studies (B3461045) in Spain, with a minimum neurological follow-up of 12 months. In addition, these populations will be described.
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ATTR	Transthyretin Amyloidosis
ATTR-ACT	Tafamidis Treatment Study for Patients with Transthyretin Amyloid Cardiomyopathy
ATTR-CM	Transthyretin cardiac amyloidosis
ATTR-PN	Transthyretin amyloidosis with polyneuropathy
ATTRv	Hereditary transthyretin amyloidosis
ATTRwt	Natural or wild-type transthyretin amyloidosis
CCE	Conductance Cutaneous Electrochemistry
CNS	Central nervous system
COMPASS-31	Composite Autonomic Symptom Score 31
CV	Cardiovascular
CVR-R	Coefficient of Variation of the R-R interval
eGFR	Estimated Glomerular Filtration Rate
EMG	Electromyogram
HF	Heart failure
LTE	ATTR-ACT Long-term Extension Study
mBMI	Modified body mass index
NCS	Nerve conduction studies
NIS	Neuropathy Impairment Score
NIS-LL	Neuropathy Impairment Score Lower Limbs
Norfolk QoL-DN	Norfolk Quality of Life-Diabetic Neuropathy

PN	Polyneuropathy
PND	Polyneuropathy Disability Score
QoL	Quality of Life
SCR	Sympathocutaneous response
TTR	Transthyretin

3. RESPONSIBLE PARTIES

Name	Job title	Affiliation	Address
PPD	Section Head	PPD	
PPD	Attending Physician	PPD	
PPD	Sr. Medical Advisor	PPD	
PPD	Sr. Medical Advisor		

Principal Investigators

They will be included as a stand-alone document in Annex 1.

Country Coordinating Investigators

The scientific coordinators will be responsible for maintaining the methodological rigor of the study, both in the design phase, as well as in the evaluation of the outcomes and in the preparation of the final report. They will ensure the ethical development of the study by maintaining scientific support to all participating physicians until the publication of the study outcomes:

Name	Job title	Affiliation	Address
PPD	Section Head	PPD	
PPD	Attending Physician	PPD	

4. ABSTRACT

Title: "Tafamidis 61mg, Outcomes in ATTR Amyloidosis with Neurological and Multisystemic Involvement - TRAMA." B3461104

Hypotheses and Objectives: Tafamidis free acid 61 mg has been shown (compared to placebo) to reduce the combination of all-cause mortality and the frequency of cardiovascular-related (CV) hospitalizations, as well as to slow the decline in functional capacity and quality of life (QoL) of patients with ATTR-CM of hereditary or wt origin. In this study the hypothesis is that tafamidis free acid 61 mg reduces the progression of neurological variables in ATTRv and ATTRwt patients with neurologic involvement.

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EVALUATING IEC: PPD

Sponsor: PPD

- Protocol Version 1.0. Date: February 17, 2022

Contact person: PPD. Sr. Medical Advisor Pfizer S.L.U.

5. AMENDMENTS AND UPDATES

Not applicable

CCI

CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]022

7. RATIONALE AND BACKGROUND

Transthyretin amyloidosis (ATTR) is a rare, progressive, clinically heterogeneous, and life-threatening disease caused by pathogenic mutations in the transthyretin (*TTR*) gene, resulting in the hereditary form (ATTRv), or due to factors related to aging, resulting in the natural or wild-type form (ATTRwt) of the disease. (Adams D, et al; Nativi Nicolau JN, et al)[1,2]

ATTR is a systemic disease in which deposition of TTR amyloid insoluble fibers can occur in multiple tissues, including the peripheral nervous system, heart, kidneys, gastrointestinal tract, and eyes, resulting in, as most common phenotypes, peripheral and/or autonomic polyneuropathy (ATTR-PN), restrictive cardiomyopathy (ATTR-CM), or a mixed phenotype (Adams D, et al)[1]. More than 140 mutations in the *TTR* gene have been described, with different phenotypes based on the mutation that the patient has (Adams D, et al)[1]. However, with disease progression, unique phenotypes generally become mixed phenotypes where cardiomyopathy can be accompanied by polyneuropathy and vice versa. In the case of ATTRwt, although the disease usually manifests with cardiac symptomatology, patients may present with sensory-motor and autonomic neurological disturbances, which in any case are less prominent in the clinical condition (Nativi Nicolau JN, et al)[2].

Cardiac transthyretin amyloidosis (ATTR-CM) is caused by extracellular deposition of TTR amyloid fibers in the heart, both in the ATTRwt form and in the ATTRv form, resulting in restrictive cardiomyopathy that clinically manifests as heart failure (HF) (Ruberg FL, et al)[3]. At least 22 mutations associated with ATTR-CM have been described, with Val122Ile, Thr60Ala, Leu111Met and Ile68Leu being the most common mutations (Rowczenio DM, et al; Caponetti AG, et al; González-Moreno J, et al)[4-6].

Globally, the inherited form of the disease can occur in both endemic and non-endemic areas. In Spain at the national level, there are two endemic foci where the prevalence of the disease is higher: Palma de Majorca and Huelva. There is currently little information on the clinical profiles of patients in Spain. The majority of the information is from endemic areas, while data from non-endemic areas remains scarce (González-Moreno J, et al; Silva Hernández, et al; Álvarez-Rubio J, et al.)[6-8]. Regarding neurologic involvement in ATTRwt patients, few descriptive and prevalence data are published internationally and all point to the need for a multidisciplinary

approach at follow-up (González-Moreno J, et al; Kharoubi M, et al; Wajnsztajn Yungher F, et al; Russell A, et al; Papagianni A, et al; Kleefeld F, et al)[5, 9-13].

Recently published data on the demographics and clinical characteristics of clinically overt Spanish patients from the Transthyretin Amyloidosis Outcomes Survey (THAOS), a global, multicenter, longitudinal, observational survey of ATTR patients and asymptomatic carriers, shows phenotypic heterogeneity associated with this disease in Spain (González-Moreno J, et al)[6]. Specifically, for patients carrying the Val122Ile variant, only 20% had a purely cardiac phenotype, while many had a neurological phenotype (40%) or mixed phenotype (40%). On the other hand, most patients with ATTRwt had a mixed phenotype (64.9%), whereas only one third had purely cardiac (22.8%) or neurological (12.3%) phenotype. The results of this analysis highlight the importance of a multidisciplinary approach and the need for a comprehensive neurological and cardiological assessment in both ATTRv and wt patients (González-Moreno J, et al)[6].

Tafamidis is a benzoxazole derivative without nonsteroidal anti-inflammatory activity that binds to TTR thyroxine binding sites with high affinity and slectivity. This leads to inhibition of dissociation of TTR tetramer into monomers, preventing the formation of amyloid fibers (Bulawa CE, et al)[14]. Tafamidis 20 mg has been shown to slow the progression of peripheral neurological deterioration in patients with ATTR polyneuropathies (ATTR-PN) at stage 1 (Coelho T, et al)[15] and has been approved in Spain since 2011 for the treatment of transthyretin amyloidosis in adult patients with stage 1 polyneuropathy to delay peripheral neurological impairment (Information available on AEMPS)[16].

In the clinical trial to evaluate the safety and efficacy of tafamidis in transthyretin cardiac amyloidosis (ATTR-ACT), tafamidis at a dose of 20 mg and 80 mg (4 x 20 mg) was shown (compared to placebo) to reduce the combination of all-cause mortality and the frequency of cardiovascular-related (CV) hospitalizations, as well as to slow down the decline in functional capacity and quality of life (QoL) of patients with ATTR-CM of hereditary origin or wt (Maurer MS, et al)[17]. Based on these outcomes, tafamidis obtained FDA and EMA approval for the treatment of patients with ATTR-CM (Information available at: AEMPS; FDA)[18,19].

Upon completion of the ATTR-ACT study, patients had the option to participate in the extension study, LTE (NCT02791230)[20] (B3461045), in which patients could be treated with tafamidis for an additional 60 months (Damy T, et al)[21]. In the LTE, patients who in the ATTR-ACT study received tafamidis continued to receive the same dose, while patients who received placebo were randomly reassigned to receive tafamidis 80 mg or 20 mg at a 2:1 ratio. Following the July 20, 2018 protocol addendum, all patients were switched to 61 mg of tafamidis free acid, a new single capsule formulation that is bioequivalent to 80 mg of tafamidis meglumine used in the ATTR-ACT (Lockwook PA, et al)[22]. Published outcomes show that tafamidis 80 mg/61 mg has greater efficacy by reducing all-cause mortality by 30% versus tafamidis 20 mg (Damy T, et al)[20].

In a retrospective study conducted in 210 patients with ATTRv in treatment with tafamidis 20 mg and with a follow-up of 18-66 months, it was observed that patients classified as non-responders had lower drug concentrations. The outcomes of this study support the hypothesis that ATTRv patients with polyneuropathy may benefit from a higher dose of tafamidis (Monteiro C, et al)[23].

Due to the phenotypic heterogeneity of ATTR patients and the growing demand for real-world data on the effect of tafamidis 61 mg in patients with systemic involvement, our objective is to conduct a retrospective study to evaluate the efficacy of tafamidis 61 mg in non-cardiac variables in patients with ATTRv and ATTRwt, included in the ATTR-ACT (B3461028) and LTE (B3461045) in Spain. To do this, extra-cardiac clinical data will be collected throughout the follow-up and treatment period with tafamidis 61 mg, in order to evaluate the efficacy of treatment in ATTR patients with neurologic involvement.

To date, little information has been published on the demographic and clinical characteristics of clinically overt Spanish ATTR patients (González-Moreno J, et al; Silva Hérnandez, et al; Álvarez-Rubio J, et al.)[6-8], and even less international data have been published on neurologic involvement in ATTRwt patients (González-Moreno J, et al; Kharoubi M, et al; Wajnsztajn Yungher F, et al; Russell A, et al; Papagianni A, et al; Kleefeld F, et al)[6, 9-13]. In addition, this study will provide an overview of Spanish patients with mixed phenotype and provide real-world data on the deterioration of polyneuropathy and management of ATTRwt patients.

There is currently no published data on the use of tafamidis free acid 61 mg in patients with ATTR-PN, therefore this study addresses an unmet medical need and may yield on the efficacy of tafamidis free acid 61 mg in patients with mixed phenotype ATTRv and in ATTRwt patients with neurologic involvement.

8. RESEARCH QUESTION AND OBJECTIVES

Based on the outcomes from previous studies (Coelho T, et al; Maurer MS, et al)[15,17], the **hypothesis** of the present study is that tafamidis free acid 61 mg decreases the progression of polyneuropathy caused by transthyretin amyloidosis in ATTRv and ATTRwt patients with neurological or mixed phenotype.

The study's **primary objective** is:

- To determine the efficacy of tafamidis free acid 61 mg in ATTRv patients with neurologic involvement included in studies B3461028 and/or LTE (B3461045) in Spain through changes in the NIS scale at 12 months.

The **secondary objectives** of this study are:

- To determine the efficacy of tafamidis 61 mg in ATTRv patients with neurologic involvement included in studies B3461028 and/or LTE (B3461045) in Spain using additional non-cardiac variables at 6, 12, 18, 24 and 36 months after the start of treatment.
- To determine the efficacy of tafamidis free acid 61 mg in ATTRwt patients with neurological symptoms included in studies B3461028 and/or LTE (B3461045) in Spain, through non-cardiac variables at 6, 12, 18, 24 and 36 months after treatment initiation.
- To describe the extra-cardiac characteristics of ATTRv and ATTRwt patients included in studies B3461028 and/or LTE (B3461045) in Spain with mixed phenotype treated with tafamidis free acid 61 mg.

9. RESEARCH METHODS

9.1. Study design

Retrospective, multicenter, non-interventional, observational and descriptive study.

It will by no means interfere with the investigator's decision on the most appropriate medical care or treatment for the patient or carrier.

The variables collected are consistent with the objectives of the study and will be described in more detail in Section 9.3:

Primary objective	**Primary variables**
To determine the efficacy of tafamidis free acid 61 mg in ATTRv patients with neurologic involvement included in studies B3461028 and/or LTE (B3461045) in Spain through changes in the NIS scale at 12 months.	Neuropathy Impairment Score (NIS)
Secondary objectives	**Secondary variables**
To determine the efficacy of tafamidis 61 mg in ATTRv patients with neurologic involvement included in studies B3461028 and/or LTE (B3461045) in Spain using additional non-cardiac variables at 6, 12, 18, 24 and 36 months after the start of treatment.	- NIS at 6, 18, 24 and 36 months - NIS-LL, Norfolk QoL-DN, COMPASS-31 and FAP-RODs, FAP - % of patients who do not have stage progression in the PND score

	- % of patients responding to treatment (defined as <4p in NIS and <2p in NIS-LL) - R-R Range Variability - mBMI - Amplitude of the potentials measured in sural sensory and ulnar, tibial and peroneal motor NCS
To determine the efficacy of tafamidis free acid 61 mg in ATTRwt patients with neurological symptoms included in studies B3461028 and/or LTE (B3461045) in Spain, through non-cardiac variables at 6, 12, 18, 24 and 36 months after treatment initiation.	- NIS, NIS-LL, Norfolk QoL-DN, COMPASS-31 and FAP-RODs, FAP - % of patients who do not have stage progression in the PND score - % of patients responding to treatment (defined as <4p in NIS and <2p in NIS-LL) - R-R Range Variability - mBMI. - Amplitude of the potentials measured in sural sensory and ulnar, tibial and peroneal motor NCS
To describe the extra-cardiac characteristics of ATTRv and ATTRwt patients included in studies B3461028 and/or LTE (B3461045) in Spain with mixed phenotype treated with tafamidis free acid 61 mg.	- Demographic variables - Age of onset symptoms and at diagnosis - Neurological and extra-cardiac clinical variables

This study, despite the limited sample size, will provide data on the efficacy of tafamidis free acid 61 mg in hereditary ATTR and wt patients with neurologic involvement.

9.2. Setting

The current study population consists of ATTRv and ATTRwt patients who have participated in studies B3461028 and B3461045 in Spain, with cardiac and neurologic involvement receiving or have received tafamidis free acid 61 mg for at least 12 months, and who are in neurological

follow-up for no less than 12 months. To our knowledge, 17 ATTRv patients have been included in these studies.

Individuals participating in the TRAMA study must meet all of the inclusion and none of the exclusion criteria described in Section 9.2.1.

9.2.1. Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Be of legal age (>18 years).

2. Have participated in studies B3461028 and/or B3461045 in Spain.

3. Have been treated for at least 12 months with tafamidis free acid 61 mg.

4. Have a minimum of 12 months of neurological follow-up after starting treatment with tafamidis free acid 61 mg and have data from previous neurological evaluation or at the time of starting treatment with tafamidis free acid 61 mg.

5. Have been diagnosed with ATTR amyloidosis polyneuropathy (ATTR-PN), based on any of the following criteria:

    a. Decreased amplitude in EMG studies, at least two nerves below normal, excluding median, or other nerve entrapment sites.

    b. A reduction in amplitude by more than 50% by at least two nerves above the patient's baseline value, excluding the median.

    c. Two different altered fine fiber tests (Sudoscan, CRS, RR interval variability, skin biopsy...).

    d. A clinic compatible with small fiber neuropathy (painful or dysautonomic) and an altered fine fiber test.

9.2.2. Exclusion criteria

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

1. Treatment with tafamidis free acid 61 mg for less than 12 months.

2. Not having a minimum of 12 months of neurological follow-up after starting treatment with tafamidis free acid 61 mg.

3. Etiological diagnosis of polyneuropathy other than ATTR.

9.3. Variables

The variables to be collected from each patient at participating sites will be:

- Clinical parameters available in their medical history in the 12 months prior to their inclusion in studies B3461028 and/or LTE (B3461045).
- Clinical parameters available in their medical history at the time of inclusion in studies B3461028 and/or LTE (B3461045) (last visit to the site before inclusion in the study).
- Routine follow-up visits (up to the last available visit prior to enrollment in the TRAMA study).

The variables to be collected from each individual's medical history during the course of this study will be:

- **Treatment-related variables**:
    - Date of consent signature for entry into study B3461028 and B3461045
    - ATTR Treatment Start Date:
        - Initiation of treatment with commercial medication (tafamidis 20 mg)
        - Treatment regimen in the trial of ATTR-ACT or LTE tafamidis 20 mg
        - Treatment regimen in the ATTR-ACT or LTE tafamidis 80 mg or 61 mg trial
    - Patient is currently on treatment with tafamidis free acid 61 mg (if not, specify stop date)

- **Demographic variables**:
    - Age, gender
    - Genotype: mutations (homozygosis/heterozygosis) or wt
    - Age of disease onset (in order to characterize whether the disease onset was neurological or cardiological and to understand why it was not treated with available therapeutic options)
    - First disease-related sign or symptom
    - Age at disease diagnosis

- **Variables collected at each follow-up visit**:
    - **Extra-cardiac 'red flags' medical history**:
        - Carpal tunnel syndrome (if yes, if there was a surgery/date)
        - Lumbar stenosis
        - Gastrointestinal disturbances: diarrhea/constipation, early satiety

- Urological disturbances: urinary tract infections, urinary incontinence, urinary infections, incomplete emptying sensation
- Ophthalmological disturbances
- Central nervous system (CNS) disturbances (seizures, stroke or transient ischemic attack, cognitive impairment)
- Symptoms of autonomic neuropathy: impaired sweating, sexual dysfunction, orthostatic hypotension
- Symptoms of peripheral neuropathy (allodynia, paresthesia, hyperalgesia...)
- Unintentional weight loss

- Modified Body Mass Index (mBMI)

- Neurological variables:

  - NIS (*Neuropathy Impairment Score*)
  - NIS-LL (*Neuropathy Impairment Score Lower Limbs*)
  - PND (*Polyneuropathy disability score*)
  - FAP *(Family Amyloidotic polyneuropathy stage*)

- Neurophysiological variables:

  - NCS (EMG): sural sensory nerves, ulnar, tibial and peroneal motor
  - CCE - Sudoscan (feet and hands, if available)
  - R-R Range Variability

- Scales:
  - Norfolk QoL-DN (*Norfolk Quality of Life-Diabetic Neuropathy*)
  - FAP-RODS (*Familial Amyloid Polyneuropathy Specific Rasch-Built Overall Disability Scale*)
  - COMPASS-31 (*Composite Autonomic Symptom Score 31*)

- Renal Assessment Variables:
  - Proteinuria, albuminuria/microalbuminuria; eGFR
  - Creatinine Clearance

- Ophthalmologic Assessment Variables:
  - Intraocular pressure
  - Glass opacity classification

Variable	Role	Source Document(s)	Operational Definition
Date of birth	Baseline Characteristic	Medical Record	The investigator will collect the data in the CRF reflecting the information included in the medical record
Sex			
Genotype: mutation (homozygous/heterozygous) or wt			
Age at onset of the disease	Subgroup Identifier	Medical Record	The investigator will collect the data in the CRF reflecting the information included in the medical record
First sign or symptom of disease			
Age at disease diagnosis			
Date of consent signature for entry into study B3461028 and B3461045	Subgroup Identifier	Medical Record	The investigator will collect the data in the CRF reflecting the information included in the medical record
ATTR Treatment Start Date			
Treatment regimen in the trial of ATTR-ACT origin (tafamidis 80 mg or 61 mg)			
Carpal tunnel syndrome (if yes, if there was a surgery/date)	Result	Medical Record	The investigator will collect the data in the CRF reflecting the information included in the medical record
Lumbar stenosis			
Gastrointestinal disturbances: diarrhea/constipation, early satiety			
Urological disturbances			
Ophthalmological disturbances			
Central Nervous System (CNS) Disorders			
Symptoms of autonomic neuropathy: impaired sweating, sexual dysfunction, orthostatic hypotension			
Symptoms of peripheral neuropathy (allodynia, paresthesia, hyperalgesia...)			
Unintentional weight loss			
mBMI mBMI (modified BMI) corrects hypoalbuminemia effects, thus better reflecting nutritional health (mBMI=BMI x albumin level)	Result	Medical Record	The investigator will collect the data in the CRF reflecting the information included in the medical record or calculated from the medical record data

NIS NIS (*Neuropathy Impairment Score*) is a clinically important, sensitive measure of individual neurological function, assessing sensory function, reflexes, and muscle weakness	Result	Medical Record	The investigator will collect the data in the CRF reflecting the information included in the medical record or calculated from the medical record data
NIS-LL NIS-LL (*Neuropathy Impairment Score Lower Limbs*) is a clinically important, sensitive measure of neurological function in individuals, assessing sensory function, reflexes, and muscle weakness of the lower limbs			
PND PND (*Polyneuropathy disability score*) is a simple staging system according to the degree of neuropathic dysfunction and its impact on ambulation			
FAP FAP (*Family Amyloidotic polyneuropathy stage*) is a staging system based on symptom severity and disease progression			
NCS (EMG): sural sensory, ulnar, tibial and peroneal nerves	Result	Medical Record	The investigator will collect the data in the CRF reflecting the information included in the medical record
CCE - Sudoscan (feet and hands) Electrochemical Cutaneous Conductance allows us to measure autonomic sudomotor function in a non-invasive, rapid and accurate manner			
CVR-R The coefficient of variation of the R-R interval is a measure of cardiovascular autonomic dysfunction. It is calculated as the standard deviation percentage of the R-R intervals divided by their mean			

Norfolk QoL-DN Norfolk Quality of Life Questionnaire for Diabetic Neuropathy is a standardized and validated instrument that assesses the effect of polyneuropathy on the functionality and quality of life of the individual	Result	Medical Record	The investigator will collect the data in the CRF reflecting the information included in the medical record
FAP-RODS FAP-RODS (*Familial Amyloid Polyneuropathy Specific Rasch-Built Overall Disability Scale*) is a questionnaire that assesses the effect of neuropathy on daily activities			
COMPASS-31 COMPASS-31 (*Composite Autonomic Symptom Score 31*) is a questionnaire designed to assess the severity and functional ability in patients with autonomic dysfunction			
Proteinuria	Result	Medical Record	The investigator will collect the data in the CRF reflecting the information included in the medical record
Albuminuria/microalbuminuria levels			
eGFR (estimated Glomerular Filtration Rate)			
Creatinine Clearance			
Intraocular pressure	Result	Medical Record	The investigator will collect the data in the CRF reflecting the information included in the medical record
Glass opacity classification			

9.4. Data source

The source document used will be electronic or physical medical record of the patient.

9.5. Study size

The population of this study consists of the ATTRv and ATTRwt patients included in studies B3461028 and B3461045 in Spain, who present with multisystem involvement (cardiac and neurological), who are currently receiving or have received treatment with tafamidis free acid 61 mg for at least 12 months; and who have a neurological follow-up of at least 12 months. To our knowledge, [redacted] ATTRv patients have been included in studies B3461028 and B3461045 studies in

Spain. Patients who respond to the inclusion criteria are estimated to be [redacted] with ATTRv and [redacted] with ATTRwt.

9.6. Data management

The investigator will collect data from patients included in an electronic Case Report Form specially designed for this study.

The number of patients will be a correlative number without any identifying value.

The information will be stored in a database which will in turn be associated with a file, detailing the permissions within the database.

9.6.1. Case report forms (CRFs)/Data collection tools (DCTs)/Electronic data record

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

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

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

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

9.6.2. Record retention

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

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., 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.

CCI [redacted]

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

9.7. Data analysis

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

9.8. Quality control

The study will be governed by the basic ethical principles contained in the Declaration of Helsinki.

The highest levels of professional conduct and confidentiality will always be maintained and applicable national data protection laws will be followed at all times. The right to patient confidentiality is critical. The patient's identity in the study documents will be encrypted and only authorized persons will have access to personal details that could identify the patient if data verification procedures require it. The personal details that could identify the patient will always be confidential.

The investigator will collect data from patients included in a Case Report Form (CRF) specially designed for this study. The patient number to be provided will be a correlative number without any identifying value. The recruited patients will be entered via dedicated data entry software and stored in the study database. A Data Management Plan (DMP) will be developed in which we will

detail the different steps to be followed to ensure consistency of the data and to ensure data quality standards.

Random monitoring will be performed in at least 20% of sites included in the study. The study monitor will review the information recorded in the CRFs against the investigator in order to verify the data collected for all study variables.

Each participating investigator will be contacted by the study monitor whenever necessary in order to assist in the data collection process and to resolve any potential occurrences. Upon completion of the CRFs, the study monitor will review the CRFs and may ask the physicians questions (called queries) regarding the most important missing variables (according to a predefined list of key variables). In this phase, the queries will be generated electronically by 100% of the patients and the researchers must resolve them before the closure of the database. The investigator may contact the study monitor when necessary.

A personal statistical team of the CRO hired by the sponsor of the study, will be responsible for the treatment and analysis of the data collected in the CRF for subsequent statistical analysis.

9.9. Limitations of the research methods

The main limitation of the study is the small sample size. Another limitation may be related to the scarcity of the data collected during the follow-up visits, which may provide a partial view of the progression of the disease at the systemic level.
Other causes of neuropathy are also common, particularly for ATTRwt, which can reduce sample size.

9.10. Other aspects

N/A

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

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

The personal data will be stored at the study site in *encrypted electronic and* form and will be *password protected* to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study

site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. *All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code.* The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

10.2. Patient consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from patients by Pfizer is not required

10.3. Institutional Review Board (IRB) or Independent Ethics Committee (IEC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms, if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained by the investigator. Copies of IRB/IEC approvals must be forwarded to Pfizer

10.4. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well with scientific purpose, value and rigor, and follow generally accepted research practices generally and described in:

- CCI [redacted]

CCI

[redacted]

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer is obligated to report adverse events (AEs) with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE, but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the case report Form and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, at least one patient identifier (e.g., gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement "A 35-year-old female..." or "An elderly male..." Other identifiers will have been removed.

Additionally, the onset/start dates and stop dates for "Illness", "Study Drug", and "Drug Name" may be documented in month/year (mmm/yyyy) format rather than identifying the actual date of occurrence within the month /year of occurrence in the day/month/year (DD/MMM/YYYY) format.

All research staff members must complete the following Pfizer training requirements:

- *"Your Reporting Responsibilities (YRR) Training for Vendors*".

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a

record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities training materials.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In the event of any prohibition or restriction imposed (e.g., 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 a Pfizer product, Pfizer should be informed immediately.
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14. LIST

Not applicable

15. LIST OF FIGURES

Not applicable

ANNEX 1: LIST OF STAND ALONE DOCUMENTS

List of Principal Investigators.