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"TRAMA" Study

"Tafamidis 61mg, Results in ATTR Amyloidosis with Neurological and Multisystemic Involvement - TRAMA."

Code: B3461104

Final Statistical Analysis Plan

Version 2.0

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Drafted by: PPD

Date: CCI

Signature: PPD

CCI

Approved by: PPD

Date: CCI

Signature: PPD

CCI

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Glossary

Abbreviation	Meaning
ATTR	Transthyretin Amyloidosis
ATTR-CM	Transthyretin cardiac amyloidosis
ATTR-PN	Transthyretin amyloidosis with polyneuropathy
ATTRv	Hereditary transthyretin amyloidosis
ATTRwt	Natural or wild-type transthyretin amyloidosis
BMI and mBMI	Body mass index and modified body mass index
CNS	Central nervous system
COMPASS-31	Composite Autonomic Symptom Score 31
eGFR	Estimated Glomerular Filtration Rate
EMG	Electromyogram
FAP	Familial Amyloidotic Polyneuropathy stage [*sic*])
FAP-RODS	Familial Amyloid Polyneuropathy Specific Rasch-Built Overall Disability Scale
HC	Medical record
HF	Heart failure
LTE	ATTR-ACT Extension Study
LVCF	Last value carried forward
Max.	Maximum
Min.	Minimum
NCS	Nerve conduction studies
NIS	Neuropathy Impairment Score
NIS-LL	Neuropathy Impairment Score Lower Limbs
No	No. of patients
Norfolk QoL-DN	Quality of life measured by the Norfolk Quality of Life-Diabetic Neuropathy version questionnaire
PN	Polyneuropathy
PND	Polyneuropathy Disability Score
Q1	First quartile
Q3	Third quartile
SAP	Statistical Analysis Plan
SCR	Sympathocutaneous response
SD	Standard deviation
SPSS	Statistical Package for the Social Sciences
TTR	Transthyretin

1 INTRODUCTION

This document contains the Statistical Analysis Plan (SAP) for the TRAMA study.

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.

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. More than 140 mutations in the *TTR* gene have been described, with different phenotypes based on the mutation that the patient has. 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 symptoms, patients may present with sensorimotor and autonomic neurological disturbances, which in any case are less prominent in the clinical condition.

Cardiac transthyretin amyloidosis (ATTR-CM) is caused by extracellular deposition of TTR amyloid fibers at the cardiac level, both in the ATTRwt form and in the ATTRv form, resulting in restrictive cardiomyopathy that clinically manifests as heart failure (HF). At least 22 mutations associated with ATTR-CM have been described, with Val122Ile, Thr60Ala, Leu111Met and Ile68Leu being the most common mutations.

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 or Tafamidis non-free acid 61 mg in patients with mixed phenotype ATTRv and in ATTRwt patients with neurologic involvement.

2 PROTOCOL VERSION AND CRF

Protocol Version: v1.0 CCI

CRF Version: v1.0 CCI

2.1 Amendments to previous versions

Date	Sections that are modified in the PAE	Summary of changes	Reason for change
version 2.0 CCI	12.1 Primary objective	Inclusion of the definition of responder according to the scale change at 12 months compared to the initial data <4p in NIS, patients who have obtained less than 4 points in the NIS in month 12	It is included in the PAE to define the primary objective in the PAE and to be able to reflect the data in this regard in the statistical report.
version 2.0 CCI	12.2.1 Secondary objective 1	Add to the secondary objectives analysis of responders according to NIS at different months and according to the NIS-LL scale at different months, separately	It is included in the PAE to define the secondary objectives in the PAE and to be able to reflect the data in this regard in the statistical report.

3 OBJECTIVES AND DESIGN

3.1 Analysis Plan Objectives

The analysis plan proposed below details the aspects that should be known about the study and the statistical analysis methods to be used in order to apply them to the data collected and to meet the objectives of the study.

3.2 Primary and Secondary Objectives

Based on the outcomes from previous studies, 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.

3.2.1 Primary objective

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 (See B3461104_Archive Note).

3.2.2 Secondary objectives

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.

3.3 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.

4 STUDY POPULATION

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 who 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. According to the protocol, patients who meet the inclusion criteria are estimated to be: 10 with ATTRv and 10 with ATTRwt.

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

4.1 Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for this 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, etc.).

d. A clinical picture consistent with small fiber neuropathy (painful or dysautonomic) and an altered fine fiber test.

4.2 Exclusion criteria

Patients who meet 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.

5 POPULATION TO BE ANALYZED

The patient's classification is defined below based on compliance with the screening criteria:

- ***Evaluable patients*** are defined as those who meet all of the inclusion criteria and none of the exclusion criteria described in the protocol.
- ***Non-evaluable patients*** are defined as those who fail to meet any of the inclusion criteria or meet one or more exclusion criteria.

Information regarding the screening criteria in the form of a binary variable (Yes / No) is recorded on the CRF for each item described.

Several of these criteria can be checked against the data collected in the CRF. The criteria that will be verified in order to define the evaluable population are described below:

Inclusion Criteria

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

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

Age of all patients at enrollment will be checked to ensure they are 18 years old or above.

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

A check will be carried out to ensure patients have answered 'yes' to one of the following questions:

- Has the patient participated in study B3461028?
- Has the patient participated in study B3461045?

It will also be confirmed that they have collected the date of the consent indicated for the corresponding previous study.

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

The difference between the Tafamidis 61 mg end date minus its start date will be checked to ensure it is at least 12 months, or otherwise the Tafamidis 80 mg end date minus its start date is at least 12 months:

(End date* - start date* ≥ 12 months)

*Dates for Tafamidis 61 mg or 80 mg

In such cases where they are on treatment with Tafamidis 61 mg, the date of inclusion in this study will be considered as "End Date".

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.

For all patients, the difference between the last follow-up and the start of treatment with Tafamidis (61 or 80 mg) will be checked to ensure it is at least 12 months.

(Last follow-up date - treatment start date* ≥ 12 months)

*The first date of treatment with Tafamidis 61 mg or 80 mg

A check will be carried out to ensure that data is available for all patients in the following neurological variables, in the 12 months prior to inclusion in the studies (B3461028 and/or LTE B3461045) or at inclusion in the same studies (start of treatment with Tafamidis 61 mg):

- NIS (Neuropathy Impairment Score)
- NIS-LL (Neuropathy Impairment Score Lower Limbs)
- FAP (Familial Amyloidotic Polyneuropathy stage)
- PND (Polyneuropathy Disability Score)

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, etc.).

d. A clinical picture consistent with small fiber neuropathy (painful or dysautonomic) and an altered fine fiber test.

This inclusion criterion cannot be confirmed with the data collected in the CRF, so only the information collected in the yes/no variable of the screening criteria is considered.

A check will be carried out to ensure that the genotype (Mutation / Wild type) has been indicated for all patients.

Exclusion criteria

Patients who meet 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.

In this section, refer to the inclusion criterion 3 check.

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

In this section, refer to the inclusion criterion 4 check.

3. Etiological diagnosis of polyneuropathy other than ATTR.

No check with CRF.

Analyses will be performed with evaluable patients on the total population and subgroup based on genotype (ATTRv and ATTRwt).

5.1 Patient Disposition

A chart of the patients included in the study, as well as those who are not evaluable, and the reasons for this will be displayed.

6 METHODS FOR THE STATISTICAL ANALYSIS

The analysis methods to be used to achieve the study objectives and draw up the descriptive content for the variables are detailed below.

❖ UNIVARIATE ANALYSIS

Quantitative variables will be described with centralization and scattering measures (mean, SD (standard deviation), median, minimum, maximum, Q1 (first quartile), Q3 (third quartile and N).

Qualitative variables will be described by absolute and relative frequencies. Two columns of percentages will be presented: Total Percentage (Total %) and Valid Percentage (Valid %):

- Total Percentage (%): Percentage of the sum of valid responses plus missing values, i.e. of the total of the sample under study.
- Valid percentage (Valid %): Percentage of total valid responses, i.e. with data on the variable.

In subgroup analyses, only the valid % with respect to the total for each group will be presented.

For questions with more than one answer option, **multiple response** tables will be shown. Two percentage column will be shown in these tables:

- Total percentage (%) Percentage of the sum of valid responses plus missing values, i.e. of the total of the sample under study. Since it is multiple choice, the sum of percentages does not have to be 100 (the percentage may be exceeded).
- Valid percentage (%) Percentage of the number of patients with at least one given answer from among the possible answers. Since it is multiple choice, the sum of percentages does not have to be 100 (the percentage may be exceeded).

Missing data will not be attributed and will be left as lost data.

Statistical analysis of variables collected in the study will be performed using the SPSS statistical program.

NOTE 1: Due to the small number of patients available in the study, no comparisons will be made and the associated p-value will not be shown. Only descriptive analyses will be presented.

NOTE 2: The texts collected in open fields will not be grouped, other than to standardize format and spelling. If desired, any grouping must be performed by the sponsor and as an additional table to the description of what is included in the database.

6.1 Visit reassignment

6.1.1 Numerical variables at follow-up (neurological and scales)

In the section on variables in follow-up, there are visit dates and no months assigned to those visits. To avoid time variability and ensure consistency of the data, for each quantitative follow-up variable, the following procedure will be calculated. All values will be assigned, as of the follow-up date, weighing the assignments based on the recorded follow-ups.

1. Months between visits:

   Firstly, the date difference between the first follow-up and the start time will be calculated for the variable in question. Values will be assigned to those visits that are close to this difference or lower, i.e. if the difference is 25 months, visits up to Month 24 will be allocated (see note 3 below).

2. Monthly unit change (exchange rate):

$$\frac{\text{(value at follow-up visit - value at start of treatment visit)}}{\text{months between visits}}$$

3. Increment for each visit:

   Monthly unit change x 6

   Monthly unit change x 12

   Monthly unit change x 18

   Monthly unit change x 24

   Monthly unit change x 36

4. Value assigned at each visit:

   Baseline value + Increment for each visit

NOTE 3:

- In case only one follow-up is available and the total follow-ups cannot be assigned, the "last value carried forward" (LVCF) method will be used, so the last value obtained will be carried over to the end.
- If more than one follow-up is available and the difference between their dates is:
  - Less than 5 months, the value will not be allocated, as the two visits would be very close to each other.
  - Greater than 5 months and less than 10 months, the value of that follow-up will be assigned to the next follow-up pending assignment. That is, if the assignment of the first follow-up

reaches month 24, the assignment of month 36 would be considered as the value recorded in the second follow-up.

– Otherwise, if the difference is greater than 10 months, the values will be assigned with the algorithm from step 1 taking the previous follow-up as baseline.

6.1.2 Categorical variables at follow-up and all other numerical variables

For categorical variables, the procedure explained above cannot be performed; as such, for these variables, a listing of the treatment start date (or the closest date) and the date of the follow-ups recorded will be sent for subsequent assignment to the corresponding month. This would also apply to all other numerical variables not covered in the previous section (e.g. BMI, albumin, etc.), as there will be no weighted increase for these variables over the visits.

7 DATABASE LOCK AGREEMENT

If abnormal and/or inconsistent values are detected in any result table, the database will not be reopened for modification; however, the abnormal data will be highlighted, as well as its processing method (e.g. through assignment of non-existent data or deletion of the case depending on the statistical method to be used in the analysis in question).

Any modification to this table will be reflected in the report in writing, as well as the procedure followed (e.g. assignment of non-existent data, interpolation, case deletion, etc.).

For the final statistical analysis, the database will only be reopened and the study data and tables that could consequently be modified will be re-analyzed if the reconsideration of the initial analysis is evaluated jointly with the sponsor.

8 DESCRIPTIVE STATISTICAL ANALYSIS (STUDY INCLUSION)

Analyses will be performed on the total population and subgroup based on genotype (ATTRv and ATTRwt). Descriptive analyses will be presented with no comparisons between genotype groups.

8.1 Treatment-related variables

Frequencies (N. %) will be shown for the following qualitative variables:

- Has the patient participated in study B3461028? (Yes / No)
- Has the patient participated in study B3461045? (Yes / No)
- Patients who participated in the above two studies.

8.1.1 ATTR Treatment Start Date

Frequencies (N. %) will be shown for the following qualitative variables:

- Commercial medication (Tafamidis 20 mg) (Yes / No)
- Treatment regimen in ATTR-ACT (B3461028) or LTE (B341045) trial of origin (multiple choice table):
    - ATTR-ACT or LTE Tafamidis 20 mg
    - ATTR-ACT or LTE Tafamidis 80 mg
    - ATTR-ACT or LTE Tafamidis 61 mg
- Is the patient currently on Tafamidis free acid 61 mg? (Yes / No)

Descriptive statistics (Mean, SD, Median, Minimum, Maximum, Q1, Q3 and N) of the following quantitative variables will be displayed:

- Duration for the following treatments (in months):
    - ATTR-ACT or LTE Tafamidis 20 mg, calculated as end date - start date.
    - ATTR-ACT or LTE Tafamidis 80 mg, calculated as end date - start date.
    - ATTR-ACT or LTE Tafamidis 61 mg, calculated as end date - start date. If still on treatment, up to the enrollment date will be considered (enrollment date - start date).

8.2 Demographic variables

8.2.1 Demographic data

Descriptive statistics (Mean, SD, Median, Minimum, Maximum, Q1, Q3 and N) of the following quantitative variable will be shown:

- Age at enrollment (years)

Frequencies (N. %) will be shown for the following qualitative variable:

- Sex (Male / Female)

8.2.2 Disease-related data at diagnosis

Descriptive statistics (Mean, SD, Median, Minimum, Maximum, Q1, Q3 and N) of the following quantitative variables will be displayed:

- Age at onset of the disease (years)
- Age at diagnosis (years)

Frequencies (N. %) will be shown for the following qualitative variables:

- Genotype (Mutation / Wildtype):
    - Mutations (Val142Ile / Ile88Leu / Thr80Ala / Val50Met / Pro44Ser / Other) (multiple choice chart). The other specifications listed will be shown.
    - For each mutation (Homozygosis / Heterozygosis / Compound heterozygosis).

8.2.3 First disease-related sign or symptom

Frequencies (N. %) will be shown for the following qualitative variables:

- Gastrointestinal disorders (Yes / No). If yes, a multiple choice table will be shown for:
    - Diarrhea
        - Frequency (< 2/week | 2/week | ≥ 3/week)
    - Nausea/vomiting
    - Severe constipation
    - Unintentional weight loss
    - Alternating episodes of diarrhea and constipation
    - Early satiety

- Urological disturbances (Yes / No). If yes, a multiple choice table will be shown for:
    - Urinary tract infections
    - Urinary retention
    - Urinary incontinence
        - Type (stress / permanent)
- Ophthalmological disturbances (Yes / No). If yes, a multiple choice table will be shown for:
    - Vitreous opacities
    - Glaucoma
    - Conjunctival vessel changes
    - Pupillary changes
- CNS changes (Yes / No). If yes, a multiple choice table will be shown for:
    - Seizures
    - Transient ischemic attack or stroke
    - Cognitive impairment
- Autonomic neuropathy changes (Yes / No). If yes, a multiple choice table will be shown for:
    - Sweating disturbance
    - Sexual dysfunction
        - Grade (Mild / Moderate)
    - Orthostatic hypotension
        - Type (Absent / Dizziness / Syncope)
- Peripheral neuropathy abnormalities (Yes / No). If yes, a multiple choice table will be shown for:
    - Allodynia/pain
    - Loss of sensitivity to temperature
    - Paresthesia / numbness / sensory loss
- Heart disorders (Yes / No). If yes, a multiple choice table will be shown for:
    - Conduction block
    - Cardiomyopathy

- Arrhythmia
- Other. The other specifications collected in cardiac abnormalities will be shown.

- Other. The other specifications listed will be shown.

9 CLINICAL PARAMETERS

Clinical parameters available in the medical history in the 12 months before inclusion in studies B3461028 and/or LTE B3461045, or inclusion in studies B3461028 and/or LTE B3461045 (start of treatment with Tafamidis 61 mg). Each section will indicate the most recent of the two time points.

Analyses will be performed on the total population and subgroup based on genotype (ATTRv and ATTRwt). Descriptive analyses will be presented with no comparisons between genotype groups.

9.1 Neurological variables

9.1.1 NIS (Neuropathy Impairment Score)

Descriptive statistics (Mean, SD, Median, Minimum, Maximum, Q1, Q3 and N) of the following quantitative variable will be shown:

- NIS result (total score ranges from 0 to 244)

9.1.2 NIS-LL (Neuropathy Impairment Score Lower-Limbs)

Descriptive statistics (Mean, SD, Median, Minimum, Maximum, Q1, Q3 and N) of the following quantitative variable will be shown:

- NIS-LL result (total score ranges from 0 to 88)

9.1.3 FAP (Familiar Amyloidotic Polyneuropathy stage)

Frequencies (N. %) will be shown for the following qualitative variable:

- FAP result (Asymptomatic / Free ambulation or stage 1 / Supportive ambulation or stage 2 / Wheelchair-bound or bedridden or stage 3)

9.1.4 PND (Polyneuropathy Disability Score)

Frequencies (N. %) will be shown for the following qualitative variable:

- PND result (Asymptomatic / I Sensory disturbances, normal gait / II Sensory disturbances, altered gait not requiring support / IIIA Gait requiring support / IIIB Gait requiring two supports / IV Wheelchair or bedside)

9.2 Neurophysiological variables

Frequencies (N. %) will be shown for the following qualitative variables:

- Nerve conduction study (EMG)
    - Axonal / Demyelinating (Altered / Unaltered)
- Sudoscan Electrocutaneous Conductance (ECC):
- RR Interval Variability (Altered / Unaltered)

Descriptive statistics (Mean, SD, Median, Minimum, Maximum, Q1, Q3 and N) of the following quantitative variables will be displayed:

- Nerve conduction study (EMG)
    - Ulnar / peroneal CMAP amplitude (mV)
    - Ulnar / Sural SNAP amplitude (µV)
- Sudoscan Electrocutaneous Conductance (ECC):
    - Hands result (µS)
    - Feet result (µS)

9.3 Scales

9.3.1 Norfolk QoL-DN (Norfolk Quality of Life-Diabetic Neuropathy)

Descriptive statistics (Mean, SD, Median, Minimum, Maximum, Q1, Q3 and N) of the following quantitative variable will be shown:

- Norfolk QoL-DN result (range -4 to 138)

9.3.2 FAP-RODS (Familial Amyloid Polyneuropathy Specific Rasch-Built Overall Disability Scale)

Descriptive statistics (Mean, SD, Median, Minimum, Maximum, Q1, Q3 and N) of the following quantitative variable will be shown:

- FAP-RODS result (total score ranges from 0 to 68) (0=Lesser ability to perform daily activities and 68=Greater ability to perform daily activities)

9.3.3 Composite Autonomic Symptom Score 31 (COMPASS-31) autonomic symptoms questionnaire

Descriptive statistics (Mean, SD, Median, Minimum, Maximum, Q1, Q3 and N) of the following quantitative variable will be shown:

- COMPASS-31 result (total score ranges from 0 to 100) (0=Lesser severity of dysautonomia and 100=Greater severity of dysautonomia):

9.4 Renal Assessment Variables

Frequencies (N. %) will be shown for the following qualitative variables:

- Proteinuria (Yes / No)
- Albumin/Microalbuminuria (Yes / No)

Descriptive statistics (Mean, SD, Median, Minimum, Maximum, Q1, Q3 and N) of the following quantitative variables will be displayed:

- Proteinuria result (g/24h)
- Albumin / microalbuminuria result (mg/g)
- Estimated glomerular filtration rate (eGFR) (mL/min/1.73m^2)

9.5 Ophthalmologic Assessment Variables

Descriptive statistics (Mean, SD, Median, Minimum, Maximum, Q1, Q3 and N) of the following quantitative variable will be shown:

- Intraocular Pressure result (mmHg)

Frequencies (N. %) will be shown for the following qualitative variable:

- Grading of Vitreous Opacity (Altered / Unaltered)

9.6 Extra-cardiac 'red flags' in medical history:

Frequencies (N. %) will be shown for the following qualitative variables:

- Carpal tunnel syndrome (Yes / No). If yes:
  - Have you had surgery (yes / no)
- Lumbar canal stenosis (Yes / No). If yes:
  - Have you had surgery? (Yes / No)
- Gastrointestinal disorders (Yes / No). If yes, a multiple choice table will be shown for:
  - Diarrhea
    - Frequency (< 2/week | 2/week | ≥ 3/week)
  - Nausea/vomiting
  - Severe constipation
  - Unintentional weight loss
  - Alternating episodes of diarrhea and constipation
  - Early satiety
- Urological disturbances (Yes / No). If yes, a multiple choice table will be shown for:
  - Urinary tract infections. If yes, descriptive statistics (Mean, SD, Median, Minimum, Maximum, Q1, Q3 and N) of the following quantitative variable will be shown:
    - Number of infections since last visit
  - Urinary retention
  - Urinary incontinence
    - Type (stress / permanent)

- Ophthalmological disturbances (Yes / No). If yes, a multiple choice table will be shown for:
    - Vitreous opacities
    - Glaucoma
    - Conjunctival vessel changes
    - Pupillary changes
- CNS changes (Yes / No). If yes, a multiple choice table will be shown for:
    - Seizures
    - Transient ischemic attack or stroke
    - Cognitive impairment
- Symptoms of autonomic neuropathy (Yes / No). If yes, a multiple choice table will be shown for:
    - Sweating disturbance
    - Sexual dysfunction
        - Grade (Mild / Moderate)
    - Orthostatic hypotension
        - Type (Absent / Dizziness / Syncope)
- Symptoms of peripheral neuropathy:
    - Allodynia/pain (Yes / No). If yes, a multiple choice table will be shown for:
        - Upper limbs. If yes:
            - Grade (Mild / Moderate / Severe)
        - Lower limbs. If yes:
            - Grade (Mild / Moderate / Severe)

- Loss of sensitivity to temperature. If yes, a multiple choice table will be shown for:
  - Upper limbs. If yes:
    - Grade (Mild / Moderate / Severe)
  - Lower limbs. If yes:
    - Grade (Mild / Moderate / Severe)
- Paresthesia / numbness / sensory loss. If yes, a multiple choice table will be shown for:
  - Upper limbs. If yes:
    - Grade (Mild / Moderate / Severe)
  - Lower limbs. If yes:
    - Grade (Mild / Moderate / Severe)

- Muscle weakness (Yes / No). If yes, a multiple choice table will be shown for:
  - Upper limbs. If yes:
    - Grade (Mild / Moderate / Severe)
  - Lower limbs. If yes:
    - Grade (Mild / Moderate / Severe)

9.7 Modified Body Mass Index (mBMI)

Descriptive statistics (Mean, SD, Median, Minimum, Maximum, Q1, Q3 and N) of the following quantitative variables will be displayed:

- Weight (kg)
- Height (m)
- BMI (kg/m^2). A self-calculated variable is available; however, the calculation will be made using the following formula. In case of discrepancy, the latter will be considered:

$$BMI = \frac{Weight\ (kg)}{(Height\ (m))^2}$$

- Albumin level (g/dL)
- mBMI. mBMI (modified BMI) corrects hypoalbuminemia effects, thus better reflecting nutritional health. A self-calculated variable is available; however, the calculation will be made using the following formula and, in the case of discrepancy, the latter will be considered:

$$mBMI = BMI\ x\ albumin\ level \quad \left(\frac{g}{dL}\right) x10$$

Note: Some sites may not have weight and height data at all visits for self-calculation. In these cases, if the mBMI data has been directly indicated, this will be considered for the analysis.

10 VARIABLES AT FOLLOW-UP

Results will be shown at Months ***6, 12, 18, 24 and 36 after treatment initiation*** (see section 6.1 with re-assignment of visits).

Analyses will be performed on the total population and subgroup based on genotype (ATTRv and ATTRwt). Descriptive analyses will be presented with no comparisons between genotype groups.

10.1 First disease-related sign or symptom

Frequencies (N. %) will be shown for the following qualitative variables:

- Gastrointestinal disorders (Yes / No). If yes, a multiple choice table will be shown for:
  - Diarrhea
    - Frequency (< 2/week | 2/week | ≥ 3/week)
  - Nausea/vomiting
  - Severe constipation
  - Unintentional weight loss
  - Alternating episodes of diarrhea and constipation
  - Early satiety
- Urological disturbances (Yes / No). If yes, a multiple choice table will be shown for:
  - Urinary tract infections. If yes, descriptive statistics (Mean, SD, Median, Minimum, Maximum, Q1, Q3 and N) of the following quantitative variable will be shown:
    - Number of infections since last visit
  - Urinary retention
  - Urinary incontinence
    - Type (stress / permanent)
- Ophthalmological disturbances (Yes / No). If yes, a multiple choice table will be shown for:
  - Vitreous opacities
  - Glaucoma
  - Conjunctival vessel changes
  - Pupillary changes
- CNS changes (Yes / No). If yes, a multiple choice table will be shown for:
  - Seizures
  - Transient ischemic attack or stroke

- Cognitive impairment

- Symptoms of autonomic neuropathy (Yes / No). If yes, a multiple choice table will be shown for:
  - Sweating disturbance
  - Sexual dysfunction
    - Grade (Mild / Moderate)
  - Orthostatic hypotension
    - Type (Absent / Dizziness / Syncope)

10.2 Modified Body Mass Index (mBMI)

Descriptive statistics (Mean, SD, Median, Minimum, Maximum, Q1, Q3 and N) of the following quantitative variables will be displayed:

- Weight (kg)
- Height (m)
- BMI (kg/m^2). A self-calculated variable is available; however, the calculation will be made using the following formula. In case of discrepancy, the latter will be considered:

$$BMI = \frac{Weight\ (kg)}{(Height\ (m))^2}$$

- Albumin level (g/dL)
- mBMI. mBMI (modified BMI) corrects hypoalbuminemia effects, thus better reflecting nutritional health. A self-calculated variable is available; however, the calculation will be made using the following formula. In case of discrepancy, the latter will be considered:

$$mBMI = BMI\ x\ albumin\ level \quad \left(\frac{g}{dL}\right) x10$$

Note: Some sites may not have weight and height data at all visits for self-calculation. In these cases, if the mBMI data has been directly indicated, this will be considered for the analysis.

- Change, difference, of mBMI from treatment baseline value.

10.3 Neurological variables in patients

10.3.1 NIS (Neuropathy Impairment Score)

See Section 6.1.1 for numerical reassignment of visits.

Descriptive statistics (Mean, SD, Median, Minimum, Maximum, Q1, Q3 and N) of the following quantitative variables will be displayed:

- NIS result (total score ranges from 0 to 244), assigned value for each visit.
- The variable change in NIS between each of the months from start of treatment will be calculated*, which will be the variable corresponding to the increase for each visit in reassignment:
    - Month 6 - start of treatment.
    - Month 12 - start of treatment.
    - Month 18 - start of treatment.
    - Month 24 - start of treatment.
    - Month 36 - start of treatment.
- To the extent possible, paired parametric (t-test) or non-parametric (Wilcoxon) statistical tests will be performed, depending on the sample distribution, to study whether there are differences in the unit change rate for pre- and post-treatment NIS (total and subgroups).

In addition, a listing will be presented per patient for NIS: In the 12 months prior to enrollment in studies B3461028 and/or LTE B3461045 or start of treatment* and follow-up (from month 6 to month 36).

*Note: Start of treatment would refer to the clinical parameters available in the medical history in the 12 months before inclusion in studies B3461028 and/or LTE B3461045, or inclusion in studies B3461028 and/or LTE B3461045 (start of treatment with Tafamidis 61 mg). For each patient, only the most recent value will be collected.

10.3.2 NIS-LL (Neuropathy Impairment Score Lower-Limbs)

See Section 6.1.1 for numerical reassignment of visits.

Descriptive statistics (Mean, SD, Median, Minimum, Maximum, Q1, Q3 and N) of the following quantitative variables will be displayed:

- NIS-LL result (total score ranges from 0 to 88), assigned value for each visit.
- Increase for each visit (monthly unit change x month).
- To the extent possible, parametric (paired t-test) or non-parametric (Wilcoxon) statistical tests will be performed, depending on the sample distribution, to study whether there are differences in the unit change rate for pre- and post-treatment NIS-LL (total and subgroups).

10.3.3 FAP (Familiar Amyloidotic Polyneuropathy stage)

Frequencies (N. %) will be shown for the following qualitative variable:

- FAP (Yes / No)
- FAP result (Asymptomatic / Free ambulation / Supportive ambulation / Wheelchair-bound or bedridden)

10.3.4 PND (Polyneuropathy Disability Score)

Frequencies (N. %) will be shown for the following qualitative variable:

- PND (Yes / No)
- PND result (Asymptomatic / Free ambulation / Supportive ambulation / Wheelchair-bound or bedridden)

10.4 Neurophysiological variables

Frequencies (N. %) will be shown for the following qualitative variables:

- Nerve conduction study (EMG)
    - Axonal / Demyelinating (Altered / Unaltered)
- Sudoscan Electrocutaneous Conductance (ECC):
- RR Interval Variability (Altered / Unaltered)
    - Contingency (descriptive) table of RR interval variability with pre-treatment and follow-up data.

Descriptive statistics (Mean, SD, Median, Minimum, Maximum, Q1, Q3 and N) of the following

quantitative variables will be displayed:

- Nerve conduction study (EMG)
    - Ulnar / peroneal CMAP amplitude (mV)
    - Ulnar / Sural SNAP amplitude (µV)
- Sudoscan Electrocutaneous Conductance (ECC):
    - Hands result (µS)
    - Feet result (µS)
- Change, difference, from values indicated at start of treatment:
    - Ulnar / peroneal CMAP amplitude
    - Ulnar / Sural SNAP amplitude
    - CCE by Sudoscan (hands and feet)

10.5 Scales

See Section 6.1.1 for numerical reassignment of visits.

10.5.1 Norfolk QoL-DN (Norfolk Quality of Life-Diabetic Neuropathy)

Descriptive statistics (Mean, SD, Median, Minimum, Maximum, Q1, Q3 and N) of the following quantitative variable will be shown:

- Norfolk QoL-DN result (value assigned at each visit).
- Increase for each visit (monthly unit change x month).
- To the extent possible, parametric (paired t-test) or non-parametric (Wilcoxon) statistical tests will be performed, depending on the sample distribution, to study whether there are differences in the unit change rate for pre- and post-treatment Norfolk QoL-DN (total and subgroups).

10.5.2 FAP-RODS (Familial Amyloid Polyneuropathy Specific Rasch-Built Overall Disability Scale)

Descriptive statistics (Mean, SD, Median, Minimum, Maximum, Q1, Q3 and N) of the following quantitative variable will be shown:

- FAP-RODS result (total score ranges from 0 to 68) (0=Lower ability to perform daily activities and 68=Greater ability to perform daily activities) (value assigned at each visit).
- Increase for each visit (monthly unit change x month).
- To the extent possible, parametric (paired t-test) or non-parametric (Wilcoxon) statistical tests will be performed, depending on the sample distribution, to study whether there are differences in the unit change rate for pre- and post-treatment Norfolk QoL-DN (total and subgroups).

10.5.3 Composite Autonomic Symptom Score 31 (COMPASS-31) autonomic symptoms questionnaire

Descriptive statistics (Mean, SD, Median, Minimum, Maximum, Q1, Q3 and N) of the following quantitative variable will be shown:

- COMPASS-31 result (total score ranges from 0 to 100) (0=Lesser severity of dysautonomia and 100=Greater severity of dysautonomia) (value assigned at each visit).
- Increase for each visit (monthly unit change x month).
- To the extent possible, parametric (paired t-test) or non-parametric (Wilcoxon) statistical tests will be performed, depending on the sample distribution, to study whether there are differences in the unit change rate for pre- and post-treatment COMPASS-31 (total and subgroups).

10.6 Renal Assessment Variables

Frequencies (N. %) will be shown for the following qualitative variables:

- Proteinuria (Yes / No)
- Albumin/Microalbuminuria (Yes / No)

Descriptive statistics (Mean, SD, Median, Minimum, Maximum, Q1, Q3 and N) of the following quantitative variables will be displayed:

- Proteinuria result (g/24h)
- Albumin / microalbuminuria result (mg/g)
- Estimated glomerular filtration rate (eGFR) (mL/min/1.73m^2)

10.7 Ophthalmologic Assessment Variables

Descriptive statistics (Mean, SD, Median, Minimum, Maximum, Q1, Q3 and N) of the following quantitative variable will be shown:

- Intraocular Pressure result (mmHg)

Frequencies (N. %) will be shown for the following qualitative variable:

- Grading of Vitreous Opacity (Altered / Unaltered)

11 ADVERSE EVENTS

Analyses will be performed on the total population and subgroup based on genotype (ATTRv and ATTRwt). Descriptive analyses will be presented with no comparisons between genotype groups.

11.1 Adverse events total

The categorical variables to be described (n. %) are:

- Number of patients with at least one adverse event

A listing of adverse events with the main variables will be shown.

11.2 Serious Adverse Events

The categorical variables to be described (n. %) are:

- Number of patients with at least one serious adverse event

A listing of serious adverse events with the main variables will be shown.

11.3 Related Adverse Events

The categorical variables to be described (n. %) are:

- Number of patients with at least one related adverse event related to a Pfizer drug

A listing will be shown with the main variables of adverse events related to a Pfizer drug (specifying the corresponding treatment).

12 ANALYSIS OF THE OBJECTIVES

12.1 Primary objective

"To determine the efficacy of Tafamidis free acid 61 mg in ATTRv patients with neurologic involvement included in studies B3461045 and/or LTE (B3461045) in Spain through changes in the 12-month NIS scale"

Primary variable: Neuropathy Impairment Score (NIS).

NOTE: ATTRv patients are considered to be those who have indicated "Mutation" in the genotype (Data related to the disease at diagnosis).

See resolution of this objective in 10.3.1 (month 12).

Additionally, the results will be presented for the percentage of patients responding to treatment of the change at month 12 with respect to the initial value. The N and % of patients responding to treatment will be calculated, defining responder as:

- change at 12 months compared to the initial data <4p in NIS, patients who have obtained less than 4 points in the NIS in month 12

Patients who do not meet the previous condition will be considered non-responders. If complete data is not available, the value will be left as missing.

12.2 Secondary objectives

12.2.1 Secondary objective 1

"To determine the efficacy of Tafamidis 61 mg in ATTRv patients with neurologic involvement included in studies B3461045 and/or LTE (B3461045) in Spain using additional non-cardiac variables at 6, 12, 18, 24 and 36 months after the start of treatment"

NOTE: ATTRv patients are considered to be those who have indicated "Mutation" in the genotype ("Data related to the disease at diagnosis").

Results will be presented in each month (6, 12, 18, 24 and 36) (see section 6.1 visit reassignment).

*Secondary objective 1 [*sic*: 2] variables:*

– NIS at 6, 18, 24 and 36 months (see section 10.3.1)

– NIS-LL (section 10.3.2), Norfolk QoL-DN (section 10.5.1), COMPASS-31 (section 10.5.3) and FAP-RODs (section 10.5.2), FAP (section 10.3.3)

– % of patients whose stage does not progress in the PND score (section 10.3.4). N and % of patients whose stage does not progress in the PND will also be obtained, referring to patients who do not change to higher stages compared to the start of treatment.

– % of treatment responders. N and % of responder patients will be calculated for this objective, with responder being defined as:

– **NIS:** Results will be presented in each month, defining responder as:

- change at 6 months from baseline <2p in NIS, patients who have achieved less than 2 points in the NIS.
- change at 12 months from baseline <4p in NIS, patients who have achieved less than 4 points in the NIS.
- change at 18 months from baseline <6p in NIS, patients who have achieved less than 6 points in the NIS.
- change at 24 months from baseline <8p in NIS, patients who have achieved less than 8 points in the NIS.
- change at 36 months from baseline <12p in NIS and, patients who have achieved less than 12 points in the NIS.

Patients who do not meet the previous condition in each month will be considered non-responders. If complete data is not available, the value will be left as missing.

– **NIS-LL:** Results will be presented in each month, defining responder as:

- change at 6 months from baseline <1p in NIS-LL, patients who have achieved less than 1 point in the NIS-LL at Month 6.
- change at 12 months from baseline <2p in NIS-LL, patients who have achieved less 2 points in the NIS-LL at Month 12.
- change at 18 months from baseline <3p in NIS-LL, patients who have achieved less than 3 points in the NIS-LL at Month 18.
- change at 24 months from baseline <4p in NIS-LL, patients who have achieved less than 4 points in the NIS-LL at Month 24.
- change at 36 months from baseline (<12p in NIS and <6p in NIS-LL), patients who

have achieved less than 12 points in the NIS and simultaneously less than 6 points in the NIS-LL at Month 36.

Patients who do not meet the previous condition in each month will be considered non-responders. If complete data is not available, the value will be left as missing.

– **NIS and NIS-LL:** Results will be presented in each month, defining responder as:

- change at 6 months from baseline (<2p in NIS and <1p in NIS-LL), patients who have achieved less than 2 points in the NIS and simultaneously less than 1 point in the NIS-LL at Month 6.
- change at 12 months from baseline (<4p in NIS and <2p in NIS-LL), patients who have achieved less than 4 points in the NIS and simultaneously less than 2 points in the NIS-LL at Month 12.
- change at 18 months from baseline (<6p in NIS and <3p in NIS-LL), patients who have achieved less than 6 points in the NIS and simultaneously less than 3 points in the NIS-LL at Month 18.
- change at 24 months from baseline (<8p in NIS and <4p in NIS-LL), patients who have achieved less than 8 points in the NIS and simultaneously less than 4 points in the NIS-LL at Month 24.
- change at 36 months from baseline (<12p in NIS and <6p in NIS-LL), patients who have achieved less than 12 points in the NIS and simultaneously less than 6 points in the NIS-LL at Month 36.

In this case, patients who do not meet the previous two conditions in each month will be considered non-responders. If complete data is not available (NIS and NIS-LL), the value will be left as missing.

– R-R Range Variability (section 10.4)

– mBMI (section 10.2).

– Amplitude of the potentials measured in sural sensory and ulnar, tibial and peroneal motor NCS (section 10.4)

To the extent possible, parametric (paired t-test) or non-parametric (Wilcoxon) statistical tests will be performed, depending on the sample distribution, to study whether there are differences in the unit change rate for pre- and post-treatment previous numeric variables (total and subgroups).

12.2.2 Secondary objective 2

"To determine the efficacy of Tafamidis free acid 61 mg in ATTRwt patients with neurological symptoms included in studies B3461045 and/or LTE (B3461045) in Spain, through non-cardiac variables at 6, 12, 18, 24 and 36 months after treatment initiation."

NOTE: **ATTRwt** patients are considered to be those who have indicated "Wildtype" in the genotype ("Data related to the disease at diagnosis").

Results will be presented in each month (6, 12, 18, 24 and 36) (see section **Error! Reference source not found.** visit reassignment).

*Secondary objective 1 [*sic*: 2] variables:*

– NIS (see section 10.3.1), NIS-LL (section 10.3.2), Norfolk QoL-DN (section 10.5.1), COMPASS-31 (section 10.5.3) and FAP-RODs (section 10.5.2), FAP (section 10.3.3)

– % of patients whose stage does not progress in the PND score (section 10.3.4). N and % of patients whose stage does not progress in the PND will also be obtained, referring to patients who do not change to higher stages compared to the start of treatment.

– % of treatment responders. N and % of responder patients will be calculated for this objective, with responder being defined as:

- change at 6 months from baseline (<2p in NIS and <1p in NIS-LL), patients who have achieved less than 2 points in the NIS and simultaneously less than 1 point in the NIS-LL at Month 6.
- change at 12 months from baseline (<4p in NIS and <2p in NIS-LL), patients who have achieved less than 4 points in the NIS and simultaneously less than 2 points in the NIS-LL at Month 12.
- change at 18 months from baseline (<6p in NIS and <3p in NIS-LL), patients who have achieved less than 6 points in the NIS and simultaneously less than 3 points in the NIS-LL at Month 18.
- change at 24 months from baseline (<8p in NIS and <4p in NIS-LL), patients who have achieved less than 8 points in the NIS and simultaneously less than 4 points in the NIS-LL at Month 24.

- change at 36 months from baseline (<12p in NIS and <6p in NIS-LL), patients who have achieved less than 12 points in the NIS and simultaneously less than 6 points in the NIS-LL at Month 36.

– R-R Range Variability (section 10.4)

– mBMI (section 10.2).

– Amplitude of the potentials measured in sural sensory and ulnar, tibial and peroneal motor NCS (section 10.4)

To the extent possible, parametric (paired t-test) or non-parametric (Wilcoxon) statistical tests will be performed, depending on the sample distribution, to study whether there are differences in the unit change rate for pre- and post-treatment previous numeric variables (total and subgroups).

12.2.3 Secondary objective 3

"***To describe the extra-cardiac characteristics of ATTRv and ATTRwt patients included in studies B3461045 and/or LTE (B3461045) in Spain with mixed phenotype treated with Tafamidis free acid 61 mg."***

Secondary objective 3 variables:

– Demographic variables (section 8.2.1)

– Age of onset of symptoms and at diagnosis (8.2.2)