Protocol B3461078

A SINGLE ARM, MULTICENTER, OPEN-LABEL STUDY TO EVALUATE THE EFFICACY, SAFETY, TOLERABILITY, AND PHARMACODYNAMICS OF ORALLY ADMINISTERED TAFAMIDIS MEGLUMINE IN TRANSTHYRETIN AMYLOID POLYNEUROPATHY PARTICIPANTS IN CHINA

Statistical Analysis Plan
(SAP)

Version: 3

Date: 21 Feb 2023

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 01 June 2019	Original 05 Jun 2019	N/A	N/A
2 28 Mar 2022	3 02 Sep 2021	Per protocol amendment 3	Update whole document per Protocol Amendment 3 changes.
3 20 Jan 2023	3 02 Sep 2021	Add in analysis related to COVID-19 impact	Section 2.1.2 was added back due to mistaken deletion in version 2. More details about the primary endpoint were added in Section 3.1. Add in references for some endpoints in Section 3.2 Due to COVID-19 pandemic, some patients were unable to come back for site visit. Instead, their assessments were done using alternative approach, eg, at local facility following protocol amendment 3 Appendix 9 "Alternative Measures During Public Emergencies" guidances. Thus, alternative data assessment approach is added as an additional intercurrent event. The corresponding Estimands and Analyses contents are updated. Add in Covid-19 impact analyses in Section 6.7. Add in analysis window for endpoints assessed less frequently in Appendix 1.1.

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study B3461078. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives, Endpoints, and Estimands

Objectives	Estimands	Endpoints
Primary:		
To evaluate the effect of tafamidis meglumine on clinical efficacy in ATTR-PN participants.	Descriptive statistics of the NIS-LL change from baseline at Week 72 (Month 18), regardless of whether or not participant continues with/adheres to treatment	Change from baseline NIS-LL at Week 72 (Month 18)
Secondary:		
To evaluate the efficacy, safety, tolerability, and pharmacodynamics of tafamidis meglumine in ATTR-PN participants.	Descriptive statistics of the secondary endpoints in ATTR-PN participants, regardless of whether or not participant continues with/adheres to treatment.	Efficacy: Change from baseline at follow-up visit on the following scales: • NIS-LL at other visits than Week 72 • TQOL score and 5 domains as measured by the Norfolk QOL – Diabetic Neuropathy (Norfolk QOL-DN); • Modified Body Mass Index (mBMI); • 36-item short form (SF-36); • EQ-5D-5L Index Score. Safety: Adverse events, vital signs (temperature, blood pressure, pulse rate, and respiratory rate), ECGs, ECHO, clinical laboratory evaluations. Pharmacodynamics: TTR stabilization and TTR concentration at Day 1 (baseline), Week 8, Week 12, Week 24, Week 48 and Week 72.

2.1.1. Primary Estimand(s)

The primary estimand of this study will use the treatment policy strategy and estimate the change from baseline NIS-LL at week 72 (month 18) in the ATTR-PN patients, regardless of whether an intercurrent event occurs. The estimand is defined according to the primary

objective and is in alignment with the primary endpoint. It includes the following 5 attributes:

- Population: ATTR-PN patients, as defined by the inclusion and exclusion criteria to reflect the targeted patient population
- Treatment: Oral tafamidis meglumine 20 mg soft capsules once daily;
- Variable: Change from baseline NIS-LL at week 72 (month 18);
- Intercurrent event(s): Treatment discontinuation, non-adherence to treatment, or alternative assessment approach is not considered. All data collected after treatment discontinuation or non-adherence to treatment (defined as treatment compliance of <80% before the assessment), or collected by alternative assessment approach are included.
- Population-level summary: Descriptive statistics of change from baseline NIS-LL at week 72 (month 18).

2.1.2. Secondary Estimand(s)

The secondary estimands of this study will also use the treatment policy strategy and evaluate the efficacy, safety, tolerability, and pharmacodynamics of tafamidis in China ATTR-PN patients, regardless of whether an intercurrent event occurs. The estimand is defined according to the secondary objectives and is in alignment with the secondary endpoints. It includes the following 5 attributes:

- Population: ATTR-PN patients, as defined by the inclusion and exclusion criteria, and who received the study treatment;
- Treatment: Oral tafamidis meglumine 20 mg soft capsules once daily;
- Variable: The corresponding secondary endpoint;
- Intercurrent event(s): Treatment discontinuation, non-adherence to treatment, or alternative assessment approach is not considered. All data collected after treatment discontinuation or non-adherence to treatment (defined as treatment compliance of <80% before the assessment), or collected by alternative assessment approach are included.
- Population-level summary: Descriptive statistics of variable.

2.1.3. Supplementary Estimand(s)

A supplementary estimand for the primary endpoint will use the hypothetical strategy, which differs from the primary estimand (Section 2.1.1) in the following attribute:

- Intercurrent event(s): Data after the intercurrent event, treatment discontinuation or non-adherence to treatment, if collected; or data collected by alternative assessment approach, if done, will be excluded.

2.2. Study Design

This is a post approval commitment study conducted in China. It is a single-arm, open-label, multicenter study designed to evaluate the efficacy, safety, tolerability as well as pharmacodynamics of tafamidis meglumine in ATTR-PN participants in China.

Participants will be evaluated for study eligibility during the screening period between Days -30 and Day 0. Approximately 10 - 15 participants will be enrolled. All enrolled participants will receive oral tafamidis meglumine 20 mg soft gelatin capsules once daily starting on Day 1 for 72 weeks (18 months). Site visits will be scheduled at Baseline (Day 1) and at Week 4, Week 8, Week 12, Week 24, Week 36, Week 48, Week 60, end of treatment, and Week 72 (or Early Study Discontinuation). Every 6 weeks (do not exceed 7 weeks since last confirmation) telephone contacts will be made during visits in which no investigative site visits are scheduled for assessment of adverse events, concomitant medications and investigational product compliance (between Week 12 and 24, between Week 24 and 36, between Week 36 and 48, between Week 48 and 60, and between Week 60 and 72).

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

Baseline for below endpoints is defined as the last measurement prior to dosing on Day 1 of the study. Change from baseline value is calculated by subtracting the baseline value from follow up visit value.

3.1. Primary Endpoint

- Change from baseline NIS-LL at Week 72 (Month 18)

NIS-LL will be utilized to calculate a total neuropathic deficit score for the lower limbs. In addition, subset scores for the lower limbs: muscle weakness (sum of Items 1-8), reflexes (sum of Items 9 and 10), sensation in great toe (sum of Items 11-14) will be calculated. The total NIS-LL will be calculated as the sum of the subset scores.

NIS-LL testing is performed 2 times at each visit. The average value of the 2 scores will be used for the analysis. The composite NIS-LL will be calculated by first taking the average over the two individual subset scores for muscle weakness, reflexes and sensation in great toe, for both left and right limbs, taken at least 24 hours apart within one week of each other. If one of the two individual subset scores is missing, the non-missing value is used to impute the missing value. The averages of each subset score then will be summed to obtain the composite NIS-LL score for that visit's assessment. If both individual subset scores are missing within the month assessment, the average will be missing and thus the composite NIS-LL will be missing for that visit.

3.2. Secondary Endpoint(s)

3.2.1. Efficacy Endpoints

- Change from Baseline in NIS-LL (lower limb) score at other visits than week 72;
- Change from baseline in the total quality of life (TQOL) score and 5 domains as measured by the Norfolk QOL – Diabetic Neuropathy (Norfolk QOL-DN); Refer to protocol section 9.4.1.3 for detailed calculation
- Change from baseline in modified Body Mass Index (mBMI); mBMI is calculated by multiplying the BMI (kg/height in m^2) by serum albumin level (g/L).

3.2.2. Quality of Life Endpoints

- Change from baseline in Short-Form 36 (SF-36, version 2, Acute) score; Refer to protocol section 9.4.3.1 for detailed calculation
- Change from baseline in EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) index score. Refer to protocol section 9.4.3.2 for detailed calculation.

3.2.3. Safety Endpoints

- Incidence and severity of adverse events;
- Incidence of vital sign (temperature, blood pressure, heart rate and respiratory rate) abnormalities and changes from baseline in vital sign measurements;
- Change from baseline in ECG measurements and incidence of electrocardiogram (ECG) abnormalities;
- Incidence of clinically significant changes on Echocardiography
- Change from baseline in clinical laboratory values and incidence of abnormalities;

3.2.4. Pharmacodynamics Endpoints

- TTR stabilization at Day 1 (baseline), Week 8, Week 12, Week 24, Week 48 and Week 72;
- TTR concentration at Day 1 (baseline), Week 8, Week 12, Week 24, Week 48 and Week 72.

Declaring a participant to have been “stabilized” is defined as percent stabilization equal to or greater than 32%. Refer to the separate Bioanalytical Plan as Appendix of Bioanalytical Report for calculation of percent stabilization.

3.3. Baseline Variables

- Demographic characteristics;

- Basic disease diagnosis;
- Medical history.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Population	Description
Enrolled	All participants who sign the ICD.
Efficacy	All participants who take at least 1 dose of tafamidis meglumine soft gelatin capsule 20 mg.
Safety	The same as above efficacy population.
Pharmacodynamic (PD)	All participants who take at least 1 dose of tafamidis meglumine soft gelatin capsule 20 mg and who have at least 1 TTR concentration/stabilization value.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

This is an estimation study with no statistical hypothesis nor decision rules.

5.2. General Methods

5.2.1. Analyses for Continuous Endpoints

The data for all continuous endpoints will be summarized by time point in tables containing descriptive statistics (N, mean, standard deviation, standard error of the mean, minimum, 1st, 2nd (median) and 3rd quartiles and maximum) for baseline and change from baseline for those endpoints measured at baseline.

5.2.2. Analyses for Categorical Endpoints

The data for categorical endpoints (including binary) will be summarized by contingency tables that show the counts/frequency and percentage in the various categories at each time point. For some categorical endpoints, such as the presence or severity of adverse events, contingency or frequency tables will consider the data over the entire duration of the study and will not be constructed at each time point.

The 2-sided 95% confidence interval for the proportion estimate will be calculated with Clopper-Pearson exact method.

5.3. Methods to Manage Missing Data

For the NIS-LL, Norfolk QOL-DN, SF-36 and EQ-5D-5L instruments, rules suggested by the developers of these will be followed in calculating scores when individual question/items may be missing. If these rules are not enough for calculating a score, then the endpoint will be considered to have a missing value. Missing values in any of the endpoints will not be imputed when summarizing these endpoints using descriptive statistics due to small sample size.

For safety data, missing dates and severity of adverse events will be imputed following Pfizer Reporting Standards. No imputation will be done for missing vital signs, ECG, Echocardiography, and laboratory measurements.

No imputation will be done for missing TTR concentration and modified BMI.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Change from Baseline NIS-LL at Week 72 (Month 18)

6.1.1.1. Main Analysis

- Estimand strategy: Treatment Policy (Section 2.1.1).
- Analysis set: Efficacy (Section 4). All participants who took at least 1 dose of tafamidis meglumine soft gelatin capsule 20 mg.
- Analysis methodology: Descriptive Summmary stated in Section 5.2.1 will be followed.
- Intercurrent events and missing data: All data collected after treatment discontinuation or non-adherence to treatment (defined as treatment compliance of <80% before the assessment), or collected by alternative assessment approach are included; No imputation will be done to missing data due to small sample size of the study.
- The basic summary statistics will be calculated. The 95% confidence interval will be presented for change from baseline NIS-LL at week 72 (month 18).

6.1.1.2. Supplementary Analyses

An analysis that assesses the primary endpoint using a hypothetical estimand strategy (Section 2.1.3) will be performed. It will use the same methodology and summary as the main analysis but will exclude data collected after the intercurrent events of treatment discontinuation or non-adherence to treatment (defined as treatment compliance <80% before the assessment), or by alternative assessment approach.

This study is conducted after the COVID-19 pandemic anchor date (09 January 2020 for China). The pandemic affected some patients' week 72 on-site visit around the end of 2022. Those subjects were unable to visit on site due to quarantine and travel restriction. Their week 72 visit assessments were done at local alternative facility per protocol amendment 3 Appendix 9 "Alternative Measures During Public Emergencies". In order to assess this impact, those subjects with week 72 NIS-LL data collected by local alternative facility will be excluded from the main analysis.

6.2. Secondary Endpoint(s)

No sensitivity or supplementary analysis will be done for any secondary endpoint. The main analyses are as following.

6.2.1. All other Efficacy (3.2.1) and Quality of Life Endpoints (3.2.2)

- Estimand strategy: Treatment Policy (Section 2.1.2).
- Analysis set: Efficacy (Section 4). All participants who take at least 1 dose of tafamidis meglumine soft gelatin capsule 20 mg.
- Analysis methodology: Descriptive Summmary stated in Section 5.2.1 will be followed.
- Intercurrent events and missing data: All data collected after treatment discontinuation or non-adherence to treatment, or collected by alternative assessment approach are included; Missing data will not be imputed.
- The basic summary statistics will be calculated by visit. The change from baseline over time in NIS-LL, mBMI and TQOL of Norfolk QOL-DN will be plotted graphically.

6.2.2. TTR Concentration and TTR Stabilization

- Estimand strategy: Treatment Policy (Section 2.1.2).
- Analysis set: Pharmacodynamic (Section 4). Participants must have a TTR concentration/stabilization assessment to be included.
- Analysis methodology: Descriptive Summmary stated in Section 5.2.2 will be followed.
- Intercurrent events and missing data: All data collected after treatment discontinuation or non-adherence to treatment, or collected by alternative assessment approach are included; missing data will not be imputed.
- The counts and proportion of participants who achieve TTR stabilization (ie, who has been stabilized) at the post baseline visits per SOA and its 2-sided 95% confidence interval will be presented in both table and graphically.

6.3. Other Endpoint(s)

Not applicable. There are no exploratory endpoints for this study.

6.4. Subset Analyses

No subset analysis is planned for this study.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Baseline variables will be summarized descriptively. Continuous variables will follow methods in Section 5.2.1. Categorical variables will follow methods in Section 5.2.2. Medical history will be listed by participant.

6.5.2. Study Conduct and Participant Disposition

The end of study subject disposition will be shown by subject evaluation groups. Frequency/counts will be provided for subject discontinuation(s) and study completion.

6.5.3. Study Treatment Exposure

The duration of treatment will be calculated as: date of the last dose – date of the first dose + 1. Any missed doses/off drug period will be ignored in the duration calculation. The treatment exposure will be defined as the number of days that participants took the study drug. Both will be summarized in following categories (days): 1, 2-28 (4 weeks), 29-56 (4-8 weeks), 57-84 (8-12 weeks), 85-168 (12 weeks-6 months), 169-252 (6-9 months), 253-336 (9-12 months), 337-420 (12-15 months), ≥421 (15-18 months).

Since study treatment should be taken once daily, study drug compliance will be calculated for each patient as: treatment exposure / treatment duration × 100. Compliance will be listed as both a continuous and categorical (<80%, ≥80%) endpoint.

6.5.4. Concomitant Medications and Nondrug Treatments

Concomitant medication usage by medication type will be tabulated using the WHO-Drug dictionary and listed following Pfizer Data Standard. Nondrug treatment will be listed as well.

6.6. Safety Summaries and Analyses

6.6.1. Adverse Events

Treatment emergent adverse event is defined as any adverse event started after the first dose. TEAEs will be summarized according to Pfizer Reporting Standards. The summary tables of TEAE and TEAE by System Organ Class (SOC) will be provided. The incidence and severity of TEAE will be presented by SOC and MeDRA Preferred Term (PT).

6.6.2. Vital Signs

Summary statistics for changes from baseline in vital sign parameters will be provided by visit following Pfizer Reporting Standards. Participants with abnormalities will be summarized by each vital sign parameter. Individual values for actual value will be listed.

6.6.3. Electrocardiograms (ECG)

ECG parameters (QT interval, QRS etc) in actual and change from baseline will be summarized descriptively following Pfizer Reporting Standards. In addition, the incidence of ECG abnormalities will also be summarized descriptively following Pfizer Reporting Standards.

6.6.4. Laboratory Data

The incidence of laboratory abnormalities observed at any time during the study will be tabulated following Pfizer Reporting Standards and summary statistics for changes from baseline will be provided by visit.

6.6.5. Echocardiography

The number (%) of subjects with normal, abnormal not clinically significant, abnormal clinically significant and unevaluable was summarized at each visit.

6.7. Additional Analyses Depicting COVID-19 Pandemic Impact

In order to report the impact of COVID-19 on clinical trial populations and study data, the following listings and summaries will be produced, in addition to the supplementary analysis for the primary endpoint as in Section 6.1.1.2:

- Listing of subjects with alternative facility or telehealth visits replacing site visits due to COVID-19 pandemic
- Listing of subjects with missing or non-site collected NIS-LL assessments due to COVID-19 pandemic
- A separate summary table solely for subject discontinuations from investigational product and withdrawal from study related to COVID-19 pandemic, if any, will be provided
- Protocol deviations related to COVID-19 pandemic will be summarized and listed separately. Both important and non-important PDs related to COVID-19 pandemic will be reported
- COVID-19 related AEs, if any, will be reported separately

7. INTERIM ANALYSES

No interim analysis will be conducted for this study. As this is an open label study, the sponsor may conduct reviews of the data during the course of the study for the purpose of safety assessment.

7.1. Introduction

Not applicable.

7.2. Interim Analyses and Summaries

Not applicable.

8. APPENDICES

Appendix 1. Data Derivation Details

Appendix 1.1. Definition and Use of Visit Windows in Reporting

Visit windows will be used for efficacy, PD variables, and for any safety displays that display by visit. The study day will be calculated as: date of assessment/collection – date of the first dose + 1. If two or more visits/observations fall into the same window, the

visit/observation closest to the target day should be used in the analyses. If there is a tie, the later visit should be used. All observations will, however, be included in the listings.

For assessments scheduled at baseline, week 24, 48 and 72 visits, below analysis window are used:

Visit Label	Target Day	Definition [Day Window] – Lower	Definition [Day Window] Upper
Baseline	1	Day 1 = date of first dose of study treatment taken in the study Prior to first dose of study treatment taken in the study	
Week 24	168	2	252
Week 48	336	253	420
Week 72	504	421	553

For all the other assessments, below analysis windows are applied:

Visit Label	Target Day	Definition [Day Window] – Lower	Definition [Day Window] Upper
Baseline	1	Day 1 = date of first dose of study treatment taken in the study Prior to first dose of study treatment taken in the study	
Week 4	28	2	42
Week 8	56	43	70
Week 12	84	71	126
Week 24	168	127	210
Week 36	252	211	294
Week 48	336	295	378
Week 60	420	379	462
Week 72	504	463	553