NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	Real-World Effectiveness of Tafamidis 80 mg or 61 mg on Neurologic Disease Progression in Patients with Mixed-Phenotype Variant Transthyretin Amyloid Cardiomyopathy (ATTRv-CM)
Protocol number	B3461099
Protocol version identifier	v3.0
Date	31 May 2023
Active substance	N07XX08
Medicinal product	Tafamidis
Research question and objectives	Primary objective: • To assess neurologic function before and after initiation of tafamidis, as either VYNDAQEL 80 mg (four 20-mg tafamidis meglumine capsules) orally once daily or VYNDAMAX 61 mg (one 61-mg tafamidis capsule) orally once daily, in patients with mixed-phenotype ATTRv-CM in a real-world setting Secondary objective: • To assess modified body mass index (mBMI) in patients with mixed-phenotype ATTRv-CM receiving tafamidis, as either VYNDAQEL 80 mg (four 20-mg tafamidis meglumine capsules) orally once daily or VYNDAMAX 61 mg (one 61-mg tafamidis capsule) orally once daily, in a real-world setting
Author	PPD (Main Author) PPD

	PPD

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ANOVA	Analysis of variance
ATTR-ACT	Transthyretin amyloidosis cardiomyopathy clinical trial
ATTR-CM	Transthyretin amyloid cardiomyopathy
ATTR-PN	Transthyretin amyloid polyneuropathy
ATTRv	Variant transthyretin amyloidosis
ATTRv-CM	Variant transthyretin amyloid cardiomyopathy
ATTRwt	Wild-type transthyretin amyloidosis
BMI	Body mass index
CCI	Charlson Comorbidity Index
CMTNS2	Charcot-Marie-Tooth neuropathy score v2
CI	Confidence interval
EMR	Electronic medical record
FTP	File transfer protocol
GPP	Good pharmacoepidemiology practices
HIV	Human immunodeficiency virus
ID	Identifier
IRB	Institutional review board
IP	Internet protocol
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
mBMI	Modified body mass index
NIS-CS	Neuropathy impairment score–composite score
NIS-LL	Neuropathy impairment score–lower limbs
MMRM	Mixed model repeated measures
MRC	Medical Research Council
PND	Polyneuropathy disability
REDCap	Research Electronic Data Capture

Abbreviation	Definition
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SD	Standard deviation
TTR	Transthyretin
QA	Quality assurance
QC	Quality control

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
PPD			

Additional Responsible Parties for the Study

Name, degree(s)	Job Title	Affiliation	Email Address
PPD			

4. ABSTRACT

Standalone document – Annex 1.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
Amendment 1	01/09/23	1-6, 9, 11	Administrative amendment: Number and timing of measurements changed to address data availability. Addition of CMTNS2 instrument. Updated template language for data analysis Updated AE reporting language per SOP	Change in PIs and available data. Not expecting most patients to have multiple measures before or after treatment.
Amendment 2	31 May 2023	Inclusion Criteria, Section 9.21	Changed criteria number 4 from "≥2: to "≥1"	Administrative, typographical error
Amendment 2	31 May 2023	Table 9-2, Clinical Outcomes	Deleted footnote to align with SAP	Administrative

6. MILESTONES

Milestone	Planned date
Completion of feasibility assessment	30 October 2022
Start of data collection	28 February 2023
End of data collection	01 November 2023
Final study report	01 October 2024

7. RATIONALE AND BACKGROUND

ATTR amyloidosis is a progressive, life-threatening, and heterogeneous rare disease caused by the deposition of transthyretin-derived amyloid fibrils in the peripheral nerves, heart, and other organs.[1,2] ATTR amyloidosis may arise from variants (mutations) in the transthyretin (TTR) gene (ATTRv amyloidosis), with more than 140 ATTRv genotypes having been identified,[3] or from the aggregation of non-mutated wild-type TTR (ATTRwt amyloidosis). Amyloid deposition in the peripheral nerves results in transthyretin amyloid polyneuropathy (ATTR-PN), but multiple symptoms and system involvement are hallmarks of ATTR-PN.[2,4,5] Amyloid fibril deposition in the extracellular matrix of the heart[2,6] results in ATTR-CM, which is characterized by arrhythmias and heart failure.[7,8] ATTRwt amyloidosis predominantly manifests as ATTR-CM. ATTRv amyloidosis is now widely recognized as a spectrum of disease that can manifest as polyneuropathy, cardiomyopathy, or a mixed phenotype, depending on the particular TTR variant, amyloid deposition pattern, and multisystem involvement.

Tafamidis meglumine is a first-in-class highly specific and selective stabilizer of both wild-type and amyloidogenic variants of transthyretin (TTR)[9] developed for the treatment of ATTR amyloidosis.[10] Tafamidis binds to TTR at the thyroxine-binding site and inhibits TTR tetramer dissociation, the rate-limiting step in the amyloidogenic process. By stabilizing the tetrameric native state of TTR, tafamidis increases the activation barrier associated with tetramer dissociation and therefore mimics the tetrameric-stabilization effect observed with naturally occurring protective trans-suppressor variants. Tafamidis has been extensively studied for the treatment of ATTR amyloidosis in independent development programs in ATTR-PN and ATTR-CM.

Tafamidis meglumine 20 mg was the first disease-modifying therapy approved for the treatment of ATTR-PN and is currently labeled and approved for once-daily dosing for treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment. Available in over 40 countries worldwide (excluding the United States) and marketed as VYNDAQEL, tafamidis meglumine 20 mg for treating ATTR-PN has demonstrated efficacy and safety and is backed

by a clinical development program including 1 controlled and 4 uncontrolled studies[11-14] The long-term effectiveness and safety of tafamidis in ATTR-PN has been further confirmed in real-world clinical practice, where it significantly delayed disease progression and improved overall quality of life.[15-18] As ATTR-PN is a progressive disease, early diagnosis and treatment are paramount,[5] although there are patients who continue to progress despite treatment.[14,19] In a real-world retrospective cohort study of 210 patients with hereditary ATTR amyloidosis treated with tafamidis meglumine 20 mg, tafamidis concentration (and consequently TTR kinetic stabilization) was identified as a predictor of response in a subset of patients, fueling the speculation that ATTR-PN patients might benefit clinically from a higher dose of.[19]

Tafamidis delivered as either VYNDAQEL 80 mg (four 20-mg tafamidis meglumine capsules) orally once daily or VYNDAMAX 61 mg (one 61-mg tafamidis capsule) orally once daily[20] was the first disease-modifying therapy approved for the treatment of cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization. Tafamidis is currently approved for the treatment of ATTR-CM in approximately 54 countries worldwide (including the United States). The efficacy and safety of tafamidis for treating ATTR-CM are supported by a clinical development program including one controlled and two uncontrolled studies in patients with ATTRv and ATTRwt cardiomyopathy.[21-23] The pivotal study of tafamidis in ATTR-CM, known as ATTR-ACT,[23] examined 20 mg and 80 mg (4 x 20 mg) of tafamidis meglumine with active dose groups pooled and compared with placebo for primary and secondary efficacy analyses. Both tafamidis doses significantly reduced the combination of all-cause mortality and cardiovascular-related hospitalizations over 30 months versus placebo. The individual 20-mg and 80-mg doses were further examined in post-hoc analyses of 30-month data from ATTR-ACT and interim data from the ongoing open-label long-term extension of ATTR-ACT.[24] After a median of 51 months' follow-up, patients initially treated with tafamidis 80 mg had a significant survival benefit compared with those initiated on the 20-mg dose. However, neurologic endpoints were not evaluated in the ATTR-CM development program, necessitating the use of alternative approaches to assess the potential benefit of tafamidis, as either VYNDAQEL 80 mg (four 20-mg tafamidis meglumine capsules) orally once daily or VYNDAMAX 61 mg (one 61-mg tafamidis capsule) orally once daily for delaying neurologic disease progression in ATTR amyloidosis.

Real-world data collection offers one such alternative. There are ATTRv-CM patients treated with tafamidis, as either VYNDAQEL 80 mg (four 20-mg tafamidis meglumine capsules) orally once daily or VYNDAMAX 61 mg (one 61-mg tafamidis capsule) orally once daily, who are mixed phenotype and receiving cardiologic and neurologic assessments prior to and following treatment as part of standard clinical practice. This provides the opportunity to examine the effect of tafamidis, as either VYNDAQEL 80 mg (four 20-mg tafamidis meglumine capsules) orally once daily or VYNDAMAX 61 mg (one 61-mg tafamidis capsule) orally once daily, on neurologic disease progression in these mixed-phenotype ATTRv-CM patients.

8. RESEARCH QUESTION AND OBJECTIVES

Primary Objective:

- To assess neurologic function before and after initiation of tafamidis, as either VYNDAQEL 80 mg (four 20-mg tafamidis meglumine capsules) orally once daily or VYNDAMAX 61 mg (one 61-mg tafamidis capsule) orally once daily, in patients with mixed-phenotype ATTRv-CM in a real-world setting.

Secondary Objective:

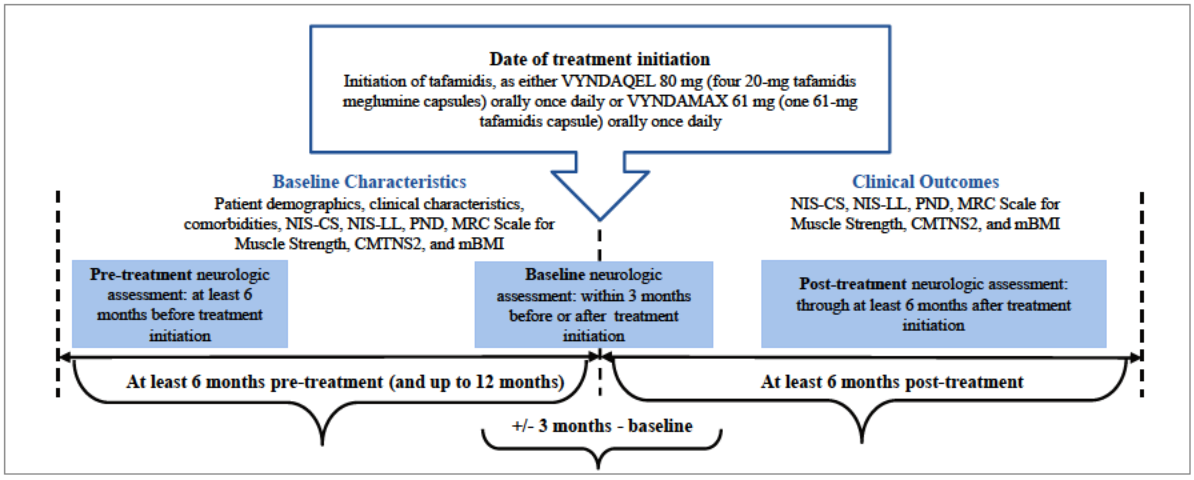
- To assess mBMI in patients with mixed-phenotype ATTRv-CM receiving tafamidis, as either VYNDAQEL 80 mg (four 20-mg tafamidis meglumine capsules) orally once daily or VYNDAMAX 61 mg (one 61-mg tafamidis capsule) orally once daily, in a real-world setting.

9. RESEARCH METHODS

9.1. Study Design

This will be an observational, retrospective cohort study using structured secondary anonymized data. Patients with mixed-phenotype ATTRv-CM receiving tafamidis, as either VYNDAQEL 80 mg (four 20-mg tafamidis meglumine capsules) orally once daily or VYNDAMAX 61 mg (one 61-mg tafamidis capsule) orally once daily for at least 6 months, will be identified. Relevant data will be extracted through at least 6 months following the initiation of tafamidis treatment.

Figure 9-1 Overview of Study Design



*Charcot-Marie-Tooth neuropathy score v2 (CMTNS2); mBMI: Modified body mass index; MRC: Medical Research Council; NIS-CS: Neuropathy impairment score–composite score; NIS-LL: Neuropathy impairment score–lower limbs; PND: Polyneuropathy disability.

9.2. Setting

The study will include patients with mixed-phenotype ATTRv-CM who are treated with tafamidis, as either VYNDAQEL 80 mg (four 20-mg tafamidis meglumine capsules) orally once daily or VYNDAMAX 61 mg (one 61-mg tafamidis capsule) orally once daily. All patients meeting the study enrollment criteria will be included.

9.2.1. Inclusion Criteria

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

1. Age ≥18 years at diagnosis.
2. Diagnosed with ATTRv-CM, mixed phenotype.
3. Treated with tafamidis (VYNDAQEL 80 mg [four 20-mg tafamidis meglumine capsules] orally once daily or VYNDAMAX 61 mg [one 61-mg tafamidis capsule] orally once daily) for ≥6 months.
4. Have had ≥1 pre- and ≥1 post-treatment neurologic assessments.*

*The pre-treatment neurological assessment will be at least 6 and up to 12 months prior to treatment initiation. The baseline assessment will be within 3 months before or 3 months after the start of tafamidis treatment. In the absence of baseline data within a+/-3 month window, structured data from exam notes may also be retrieved if available to align with real world practice. The post-treatment period will be at least 6months after treatment initiation.

Note: As this study involves anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients is not required.

9.2.2. Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:

1. History of organ transplant.
2. Wild-type TTR genotype.
3. Individuals who are non-ambulatory.
4. Prior treatment with any disease-modifying therapy (investigational or approved) alone or in combination, except tafamidis, as either VYNDAQEL 80 mg (four 20-mg tafamidis meglumine capsules) orally once daily or VYNDAMAX 61 mg (one 61-mg tafamidis capsule) orally once daily.
5. Peripheral neuropathy attributed to causes other than ATTR amyloidosis (eg, diabetes mellitus, B12 deficiency, HIV infection).

9.3. Variables

9.3.1. Exposure Variables

Tafamidis treatment will be described using the variables in the table below.

Table 9-1 Exposure Variables

Variable	Role	Data source(s)	Operational Definition
Time to treatment initiation	Exposure	Research database	Calculated as time from ATTR-CM diagnosis to tafamidis initiation
Treatment start date	Exposure	Research database	Date of tafamidis treatment initiation
Treatment end date	Exposure	Research database	Date of end of tafamidis treatment
Treatment duration	Exposure	Research database	Calculated as time from treatment initiation to the end of treatment or last visit date

9.3.2. Outcome Variable

For the primary and secondary objectives, the following clinical outcomes will be assessed. Neurologic progression scores are routinely collected in clinical practice.

Table 9-2 Clinical Outcomes

Variable	Role	Data source(s)	Operational Definition
Neurologic progression			
Neuropathy impairment score– composite score (NIS-CS)	Outcome	Research database	Data contains an assessment score for each muscle group or sensation area for motor strength/weakness, muscle stretch reflexes, and sensation. A final NIS-CS score will be calculated as a sum of these scores from the 3 sections ranging from 0 (normal) to 244 (total impairment).
Neuropathy impairment score–lower limbs (NIS-LL)	Outcome	Research database	Same as above, NIS-LL will be calculated using individual assessment scores for motor strength/weakness, muscle stretch reflexes and sensation, from lower body only, ranging 0 (normal) to 88 (total impairment).
Polyneuropathy disability (PND) score	Outcome	Research database	A scoring system of the patient's walking capacity. It consists of four stages from stage 0 (no impairment) to stage IV (confined to a wheelchair or bedridden).
Medical Research Council (MRC) Scale for Muscle Strength	Outcome	Research database	The MRC scale of muscle strength uses a score of 0 to 5 to grade the power of a particular muscle group in relation to the movement of a single joint
Charcot-Marie-Tooth neuropathy score v2 (CMTNS2)	Outcome	Research database	Composite of nine assessments: symptoms (three items), signs (four items), and neurophysiology (two items). It is designed to measure length-dependent

Variable	Role	Data source(s)	Operational Definition
			motor and sensory impairment in genetic neuropathies. Each assessment is scored on a 0 – 4 point scale, reflecting severity of impairment. Patients are classified as mild (CMTNS ≤ 10), moderate (CMTNS 11 – 20), or severe (CMTNS > 20).
Overall health			
Height	Outcome	Research database	Height in centimeter or inches
Weight	Outcome	Research database	Weight in kilograms or pounds
Body mass index	Outcome	Research database	Recorded or calculated in kg/m^2
Modified BMI (mBMI)	Outcome	Research database	Calculated as the product of BMI in kg/m^2 and serum albumin in g/L to compensate for peripheral edema.

Patient demographic and clinical characteristics to be assessed are listed in Table 9-3.

Table 9-3 Patient Demographics, Clinical characteristics, and Comorbidities

Variable	Role	Data source(s)	Operational Definition
Patient demographics			
Age	Baseline characteristic	Research database	Patient age at baseline*; age groups will be determined by distribution of age.
Gender	Baseline characteristic	Research database	Male/Female
Race	Baseline characteristic	Research database	American Indian or Alaska Native/Asian/Black or African American/Native Hawaiian or Other Pacific Islander/White
Ethnicity	Baseline characteristic	Research database	Hispanic or Latino/Not Hispanic or Latino
Clinical characteristics			
Age at ATTR-CM diagnosis	Baseline characteristic	Research database	Age at diagnosis in years
TTR genotype	Baseline characteristic	Research database	Mutation in TTR gene associated with ATTR amyloidosis (eg, Val122Ile, Val30Met, Leu58His, Leu111Met)
Family history	Baseline characteristic	Research database	No family history/Parent/Siblings/Grandparent/ Other/Unknown
Comorbidities			
Charlson Comorbidity Index (CCI)**	Baseline characteristic	Research database	Based on comorbidities present at baseline*; grouped as 0, 1, 2, 3+

*Baseline is defined as within 3 months prior to or 3 months following initiation of tafamidis. In the absence of baseline data within a +/- 3-month window, data outside this window may be used to align with real world practice.
**Individual comorbid conditions may be assessed based on feasibility assessment instead of CCI.

9.4. Data Source

The source of data for this study will be de-identified secondary data from an anonymized research database.

9.5. Study Size

No formal sample size calculation has been performed; all eligible patients treated at the study site will be included. It is estimated that at least 30 patients will be enrolled.

9.6. Data Management

Data will be transferred from the de-identified research database to OPEN Health's database server via encrypted external hard drive/disk or a secured file transfer protocol (FTP) server, which is locked in a secure room with physical access limited to server administrators. Network access to the database server will be restricted to the internet protocol (IP) addresses of project staff workstations on a limited access network behind a firewall system. Only

authorized personnel as indicated above will be provided with the password to use the media or log in to the server to access the data for analysis. The authorized personnel may download analytical datasets to their secured OPEN Health computers (encrypted and password protected). However, download to any personal computer will not be possible. Access to the received media and printed materials containing EMR data will be restricted to project staff and will be kept in a locked file cabinet. Aggregated analyses results will be presented at conferences and/or published in a journal with no patient-level data exposed.

The data will be used only for this specific study protocol. There will be no linkage of the data with any other data source. Patient IDs in the data are de-identified, and it will be impossible to trace patients' personal information (eg, name, mailing address) by using the patient ID. All analyses will be performed using Statistical Analysis System (SAS) version 9.4.

9.7. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in an 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 will be reflected in a protocol amendment.

9.8. Quality Control

To ensure programming quality and accuracy, the following steps will be taken:

- **Methodology review:** All methodology, from sample selection to variable calculation, will be discussed and reviewed at the time of project initiation.
- **Operational definitions review:** All operational definitions for calculated variables will be reviewed by the principal SAS programmer, a second SAS programmer, and Pfizer.
- **Statistical review:** The statistical methods utilized will be reviewed by a statistician as well as the SAS statistical programmer, project manager, senior scientific leader, and Pfizer.
- **Output review:** All SAS output will be initially reviewed by the SAS programmer for logic and reasonability. Output will then be reviewed by the project manager, senior scientific leader, and Pfizer. Additional reports will be run by the SAS programmer and Pfizer to ensure validation of SAS output.

During document preparation, quality control (QC) will include general proofreading and formatting, including but not limited to checks for errors related to spelling and grammar, font consistency, table/figure numbering, styles/header numbering, and general formatting/spacing. QC will also include confirming data (fact checking) and ensuring proper referencing, when applicable. For analyses and reports that utilize technical software, QC

will additionally include cross-checking internal methods/statistical review and ensuring clear presentation of findings. A corrective and preventative action plan will be part of analytic projects, with a documented deviation process and mechanisms in place to report serious deviations on the quality of/processes generating the data. The project officer or non-project senior staff member will serve as the internal resource for investigating and reporting serious deviations. The QC/quality assurance (QA) procedure will also be conducted for written communications, including meeting minutes and project-related emails, with internal team members and Pfizer.

9.9. Limitations of the Research Methods

This study will have several limitations.

First, the retrospective and observational nature of our study may be subject to unmeasured confounding. However, a longitudinal before and after study design will be used to evaluate treatment effects in the same patient group. It will also be unlikely to have unmeasured time-varying patient factors since ATTR-CM is an inexorably progressive disease caused by genetic mutation or the aggregation of non-mutated, wild-type TTR due to aging. Study results could be affected by misclassification bias due to misreporting or misdiagnosis due to the similarity of ATTR-CM to other types of heart failure.

Second, the study will be limited to ATTRv-CM patients from a single center, potentially mitigating generalization of study results to other ATTRv-CM patient populations due to different patient characteristics or local practice patterns.

Finally, ATTR-CM is a rare disease. While the inclusion of <100 patients is generally considered a relatively small sample size, it is not for a rare disease. The sample size of the previous clinical trial that established the efficacy of once-daily tafamidis 20 mg on delaying neurologic progression in ATTR-PN was also relatively small given that this is a rare disease.[11] In addition, as the study will be exploratory in general, the sample size is not expected to be a limiting factor, and this will be taken into account when reporting the results.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

This study will involve data that will exist in anonymized structured format and contain no personal patient information.

10.2. Patient Consent

As this study will involve anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients will not be required.

10.3. Institutional Review Board (IRB)/Independent Ethics Committee

The study protocol will be submitted to the local IRB to apply for an exemption/waiver from IRB review prior to data transfer.

All correspondence with the local IRB will be retained and copies of correspondence filed in accordance with good pharmacoepidemiology practices (GPP).

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor, and will follow generally accepted research practices described in Guidelines for GPP issued by the International Society for Pharmacoepidemiology, Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), and United States Food and Drug Administration Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start or a combination of existing structured data and unstructured data, which will be converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing. In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of this study will be made public by posting on clinicaltrials.gov. Further communication of these data may occur via abstracts and manuscripts.

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14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	Section 4	09 January 2023	Real-World Effectiveness of Tafamidis 80 mg or 61 mg on Neurologic Disease Progression in Patients with Mixed-Phenotype ATTRv-CM

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not required.

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

Document Approval Record

Document Name:	B3461099_Non Interventional Protocol Amendment 2 version 3.0_clean_31May2023
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PPD	31-May-2023 20:55:31	Final Approval