NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	Tafamidis Pregnancy Surveillance Study
Protocol number	B3461091
Protocol version identifier	1.0
Date	28 April 2020
EU Post Authorization Study (PAS) register number	Study not yet registered
Active substance	Tafamidis PF-06291826
Medicinal product	Vyndaqel (tafamidis meglumine) 20 mg capsules Vyndamax (tafamidis) 61 mg capsules
Product reference	Not applicable
Procedure number	Not applicable
Marketing Authorization Holder(s) (MAH)	FoldRx, a wholly owned subsidiary of Pfizer, Inc. 500 Arcola Road Collegeville PA 19426 USA
Joint PASS	No
Research question and objectives	This descriptive non-interventional study of women diagnosed with ATTR exposed to tafamidis during or within 1 month prior to pregnancy is intended to assess the risks to pregnancy outcomes and possible adverse effects on the developing fetus and neonate.

	Objectives – 1. Describe birth outcome frequency within the reported pregnancy outcomes (live full term or premature birth, spontaneous or induced abortion, and stillbirth) in women with ATTR exposed to tafamidis during or within 1 month prior to pregnancy. 2. Describe the frequency of reported fetal neonate, and infant outcomes within the reported pregnancies (major congenital malformations/anomalies [overall and specific], low birth weight, small for gestational age (SGA), preterm birth, low Apgar score at 1 and 5 minutes, and infant milestone status at 6 and 12 months) following tafamidis exposure in women ATTR during and 1 month prior to pregnancy.
Countries of study	Global
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ATTR	Transthyretin amyloidosis
ATTR-CM	Transthyretin amyloid cardiomyopathy
ATTR-PN	Transthyretin amyloid polyneuropathy
AUC	Area under the curve
CM	Cardiomyopathy
CRF	Case report form
CT	Clinical trial
DCT	Data collection tool
DSU	Drug safety unit
EDP	Exposure during pregnancy
ENCePP	European network of centres for pharmacoepidemiology and pharmacovigilance
EU	European Union
FDA	Food and drug administration
HED	Human equivalent dose
HCP	Health care professional
Leu111Met	Leucine replaced by methionine at position 111
MedDRA	Medical dictionary for regulatory activities
MRHD	Maximum recommended human dose
NIS	Non-Interventional Study
PAM	Post-authorization measure
PASS	Post-authorization safety study
PIL	Patient information leaflet
PMR	Post-marketing requirement
PN	Polyneuropathy
PSUR	Periodic safety update report
PV	Pharmacovigilance
RMP	Risk Minimization Plan
SAE	Serious adverse event
SGA	Small for gestational age
SmPC	Summary of product characteristics
TESPO	Tafamidis Enhanced Surveillance for Pregnancy Outcomes
THAOS	Transthyretin Amyloidosis Outcomes Survey
TTR	Transthyretin
TTR-FAP	Transthyretin familial amyloid polyneuropathy
US	United States

USPI	US package insert
USPPI	US patient package insert
Val30Met	Valine replaced by methionine at position 30
Val122Ile	Valine replaced by isoleucine at position 122

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Table 1. Principal Investigator of the Protocol

Name, degree	Job Title	Affiliation
Alison Flynn, RN, BSN, MBA	Clinician	Pfizer, Inc 500 Arcola Road Collegeville PA 19426 USA

Country Coordinating Investigators

Not Applicable.

3. ABSTRACT

Title: Tafamidis Pregnancy Surveillance Study

Rationale and background: VYNDAQEL® (tafamidis meglumine 20 mg capsule) once daily was first approved in the European Union (EU) for transthyretin amyloid polyneuropathy (ATTR-PN), also known as transtheyretin familial amyloid polyneuropathy (TTR-FAP) under exceptional circumstances on 16 November 2011. The product has been approved for ATTR-PN in over 40 other countries since then. The Tafamidis Enhanced Surveillance for Pregnancy Outcomes (TESPO), a worldwide approach to enhanced surveillance of pregnancy and birth outcomes in women with ATTR-PN exposed to tafamidis, was implemented as an additional pharmacovigilance activity in the EU Risk Minimization Plan (RMP), classified as a category 3 post-authorization measure (PAM), and has been in effect since 2011.

The original TESPO program was amended to broaden the scope from women with ATTR-PN to also include women with transthyretin amyloid cardiomyopathy (ATTR-CM), exposed to tafamidis and to also include all formulations and dosage forms (20 mg tafamidis meglumine and 61 mg tafamidis free acid).

On 03 May 2019, with the US approval of VYNDAQEL® once daily at a dose of 80 mg (tafamidis meglumine 4 x 20 mg capsules), and VYNDAMAX® (tafamidis 61 mg capsule) once daily for transthyretin amyloidcardiomyopathy (ATTR-CM), Food and Drug Administration (FDA) required a worldwide pregnancy surveillance study in women with ATTR exposed to tafamidis meglumine and tafamidis (henceforth collectively referred to as "tafamidis") during pregnancy to assess the risks of pregnancy complications and adverse effects on the developing fetus and neonate. To meet this post-marketing requirement (PMR 3576-1), this study will describe birth outcome frequency within the reported pregnancies in women with ATTR exposed to tafamidis during or within 1 month prior to pregnancy included in the ongoing TESPO surveillance program and/or standard exposure during pregnancy (EDP) and follow-up information collected in interventional studies.

Research Question and Objectives: This global, prospective, non-interventional study of women with ATTR exposed to tafamidis during or within 1 month prior to pregnancy is intended to assess the risks to pregnancy outcomes and possible adverse effects on the developing fetus and neonate.

The specific objectives are:

1. Describe birth outcome frequency within the reported pregnancies (live full term or premature birth, spontaneous or induced abortion, and stillbirth) in women with ATTR exposed to tafamidis during or within 1 month prior to pregnancy.

2. Describe the frequency of reported fetal, neonate and infant outcomes within the reported pregnancies (major congenital malformations/anomalies [overall and specific], low birth weight, small for gestational age (SGA), preterm birth, low Apgar score at 1 and 5 minutes, and infant milestone status at 6 and 12 months) following tafamidis exposure in women with ATTR during or within 1 month prior to pregnancy.

Population: Women diagnosed with ATTR who received tafamidis during pregnancy or who became pregnant within 1 month after discontinuation of tafamidis reported as EDP events in interventional or non-interventional clinical studies in the tafamidis development program, via spontaneous reports, solicited cases or compassionate use reports, and who agreed to release information from their obstetric and pediatric healthcare provider will be included in this study.

Study Design: This is a global, prospective, non-interventional study designed to collect and report information obtained via TESPO and/or standard EDP and follow-up information on outcomes of events of pregnancy in women with ATTR exposed to tafamidis during pregnancy or who became pregnant within 1 month after discontinuation of drug.

Variables: Variables to be evaluated in this study include patient medical /obstetrical history, pregnancy status and outcomes, and neonate and infant development status at birth, 6 and 12 months of age.

Data Sources: Events of pregnancy reported in female patients with ATTR receiving tafamidis via clinical trials, non-interventional trials, through direct contact from patients and health care professionals using the toll-free numbers provided in the labeling documents, through unsolicited requests for pregnancy safety information (via Pfizer Medical Information Department) or through contact with sales representatives. Information regarding how to contact the Sponsor (per country specific labeling guidelines) in the event of a pregnancy exposure is provided in the summary of product characteristics (SmPC), the US package insert (USPI), the patient information leaflet (PIL), and in informational materials provided (e.g., scientific meetings and direct communication) to health care professionals (HCPs).

Study Size: Sample size calculation is not applicable. In this descriptive study all female patients diagnosed with ATTR reported as having tafamidis exposure during or within 1 month of pregnancy will be included.

Data Analysis: Given the expected low number of pregnancy exposures, no formal data analysis or hypothesis testing will be conducted. Data collected on exposure and outcomes will be summarized descriptively. Women with ATTR exposed during pregnancy to concomitant medications with a known increased risk for congenital anomalies will be excluded from the descriptive summary but will be included in the study and described separately. A separate descriptive summary based on prospective and retrospective cases will be performed and submitted to the FDA. Prospective cases are defined as women who

enroll prior to the occurrence of the pregnancy outcome (live birth, miscarriage, stillbirth, pregnancy termination). Retrospective cases are defined as women who enroll or contact the registry after the pregnancy outcome has occurred (live birth, miscarriage, stillbirth, pregnancy termination). Stratified analysis of the reported pregnancy outcomes, including pregnancies in women reported prior to start of this protocol, will be performed by daily maternal dose.

Milestones: With the protocol finalized in April 2020, the trial will initiate shortly thereafter and data collection will end in June 2030. Annual interim reports and the final study report will be submitted to the FDA according to committed timelines (Interim: April 2021, April 2022, April 2023, April 2024, April 2025, April 2026, April 2027, April 2028, April 2029, April 2030; Final Report: December 2030).

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Milestone	Planned date
Start of data collection	April 2020
End of data collection	June 2030
Registration in the EU PAS register	01 March 2020
Interim study reports	April 2021, April 2022, April 2023, April 2024, April 2025, April 2026, April 2027, April 2028, April 2029, April 2030
Final study report	December 2030

6. RATIONALE AND BACKGROUND

VYNDAQEL® (tafamidis meglumine 20 mg capsule) once daily was first approved in the EU for transthyretin amyloid polyneuropathy (ATTR-PN), also known as transthyretin familial amyloid polyneuropathy (TTR-FAP) under exceptional circumstances on 16 November 2011. The product has been approved for ATTR-PN in over 40 other countries since then. TESPO, a worldwide approach to enhanced surveillance of pregnancy and birth outcomes in women with ATTR-PN exposed to tafamidis, was implemented as an additional pharmacovigilance activity in the EU Risk Minimization Plan (RMP), classified as a category 3 post-authorization measure (PAM), and has been in effect since 2011. As of 25 September 2019, there were 20 cases of exposure in utero to tafamidis, of which 13 were maternal exposure, during or within 1 month prior to pregnancy in the overall tafamidis program (clinical and non-interventional studies: Fx-005 (1); Fx1A-303 (2); Transthyretin Amyloidosis Outcomes Survey [THAOS](17).

On 03 May 2019, with the US approval of VYNDAQEL® once daily at a dose of 80 mg (tafamidis meglumine 4 x 20 mg capsules), and VYNDAMAX® (tafamidis 61 mg capsule) once daily for transthyretin amyloid cardiomyopathy (ATTR-CM), FDA required a post-marketing requirement (PMR 3576-1). To meet this post-marketing requirement (PMR 3576-1), this study will describe birth outcome frequency within the reported pregnancies in women with ATTR exposed to tafamidis during or within 1 month prior to pregnancy that are collected using the ongoing TESPO surveillance program and/or standard EDP and follow-up information collected in interventional studies.

In addition to US approval, tafamidis for the treatment of patients with ATTR-CM has been approved in Japan, United Arab Emirates, Brazil Canada, European Union, Singapore, Switzerland and Australia at this time.

This descriptive non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is a commitment to the US FDA.

6.1. Disease Background

Transthyretin amyloidosis (ATTR) is a rare protein misfolding disease with a broad spectrum of manifestations. The condition is caused by the destabilization and dissociation of the native TTR tetramer which can result in misfolding and the formation of amyloid fibrils and progressive amyloid deposition in tissues.[1,2,5,6] This can occur in amounts sufficient to impair normal functioning. The 2 major phenotypes which form the spectrum of ATTR are ATTR-PN, also referred to as TTR-FAP, which primarily affects the peripheral and autonomic nerves, and ATTR-CM which primarily affects the myocardium. These clinical manifestations may occur in isolation or together. Both result in progressively impaired function, and ultimately in death. ATTR is both a hereditary as well as an age-related disease. More than 120 TTR single site variants have been identified and associated with ATTR.

ATTR-PN is a late onset, autosomal dominant disease characterized by inexorable neurodegeneration associated with sensory loss, motor weakness and autonomic dysfunction such as dizziness, gastrointestinal disorders, sexual dysfunction and urinary incontinence.[6-11] The most common variant associated with polyneuropathy is valine replaced by methionine at position 30 (Val30Met) accounting for approximately 85% of patients worldwide.[1] Males and females are similarly affected. ATTR-PN disease usually begins in the third or fourth decade, but the onset of symptoms may be later.[2] Age of onset ranges from mid-30s in the endemic areas of Portugal and Japan to the late 50s/early 60s in Sweden and the United States. After a mean interval of 10 years from initial symptom, patients usually die from progressive and relentless worsening of the neuropathy, secondary infections, cachexia or sudden death.[2]

ATTR-CM is associated with both wild-type and genetic variants of TTR such as valine replaced by isoleucine at position 122 (Val122Ile) and leucine replaced by methionine at position 111 (Leu111Met).[1,3,9] The Val122Ile mutation allele occurs in 3.3% to 4.0% of the US African-American population,[5,6] and is exceedingly rare in White patients. ATTR-CM is currently associated with mean progression to death within 2 to 3 years (median survival 25.6 months) of diagnosis for variants and up to 5 years (median survival 43.0 months) for wild type,[7] with most patients dying from cardiac causes, including sudden death, congestive heart failure, and myocardial infarction.[8]

In wild-type disease, TTR may become structurally unstable and result in deposition of amyloid fibrils, primarily in heart tissue, and will ultimately lead to diastolic dysfunction, restrictive cardiomyopathy and heart failure.[8-11] The frequency of TTR amyloid deposition

in cardiac ventricles reported from autopsy studies in patients >80 years of age range from 1.8%[3] to 16.5%,[12] with a rate of clinical cardiac disease premortem of 34%.[12]

ATTR-CM typically occurs in patients aged 60 years or older, though the Leu111Met variant may express ATTR-CM in patients at an earlier age. ATTR-CM (both wild type and variant TTR) uniformly presents with the typical symptoms of heart failure (restrictive cardiac disease), including shortness of breath, dyspnea on exertion, orthostatic hypotension, syncope and dysrhythmias including atrial fibrillation. Signs of ATTR-CM are assessed via tests performed as part of routine heart failure assessment making the diagnosis of cardiac amyloidosis difficult, resulting in diagnosis delays, and under diagnosis of ATTR-CM. The prevalence of ATTR-CM is defined as rare, but no prevalence estimates have been published. Though prevalence of wild-type ATTR-CM is uncertain, studies using a non-biopsy approach to diagnosis, report a prevalence of 13% in heart failure patients with preserved ejection fraction, 16% in patients undergoing transcatheter aortic valve replacement for severe aortic stenosis, and 5% of ATTR-CM is associated with genetic variants of TTR such as Val122Ile and Leu111Met.

Of note, due to the typical age range for ATTR-CM patients (≥60 y.o.) the expected number of exposure during pregnancy is anticipated to be very low, due to the low number of women of child-bearing potential in this population.

6.2. Tafamidis

6.2.1. Mechanism of Action

Tafamidis is a selective stabilizer of tetrameric wild-type TTR and of amyloidogenic variants of TTR, of which Val30Met mutation (primarily affecting the peripheral nerves) and Val122Ile mutation (primarily affecting myocardium) are the most abundant. Mixed phenotypic presentations (ie, polyneuropathy and cardiomyopathy) are frequent in non-Val30Met TTR mutations. The underlying mechanism of TTR amyloid disease, regardless of the phenotypic presentation is believed to be an accelerated deposition of the unstable TTR monomers.

Tafamidis binds to the native tetrameric forms of TTR and thereby inhibits tetramer dissociation, the rate limiting step in the formation of TTR amyloid. Tafamidis has an approximate 55-hour half-life and has been demonstrated to achieve stabilization of the TTR tetramer in over 40 mutations and wild-type TTR, for which it was tested. This novel class of TTR stabilizing drug disrupts the progression of ATTR.

6.2.2. Relevant Nonclinical Findings

There was no evidence of adverse effects of tafamidis on fertility, or reproductive performance, or mating behavior in rats. In animal reproductive studies, oral administration of tafamidis meglumine to pregnant rabbits during organogenesis resulted in adverse effects on development (embryofetal mortality, fetal body weight reduction and fetal malformation) at a dose providing approximately 9 times the human exposure area under the curve (AUC) at the maximum recommended human dose (MRHD), and increased incidence of fetal skeletal variations at a dose providing equivalent human exposure (AUC) at the MRHD. Postnatal mortality, delayed male sexual maturation, and impaired learning and memory were observed in offspring of pregnant rats administered tafamidis meglumine during gestation and lactation at a dose approximately 2 times the MRHD based on body surface area (mg/m^2).

Nonclinical studies with tafamidis indicate that there are no effects on the male germ cell before conception. In toxicology studies there was no evidence of genotoxicity, no histopathological changes in testis or epididymis and no effects on male fertility at doses up to 30 mg/kg. Therefore, the risk for male-mediated developmental toxicity is considered to be low because the levels of tafamidis estimated to be transferred in semen are significantly lower than the concentrations that cause developmental toxicity in nonclinical studies.

In summary, anomalies have been observed in rabbit and rat reproductive toxicology studies. In humans, ATTR could present during the patient's reproductive years, although based on our current understanding of age of onset of disease, this is more likely for a patient with ATTR-PN rather than ATTR-CM. On account of the low prevalence of ATTR-PN and ATTR-CM (rare diseases), limited reproductive data are available in humans. There has been a low incidence of exposures reported in women with ATTR-PN in the ongoing TESPO surveillance program from clinical and NI studies over a 7-year period. Nonetheless, given that tafamidis meglumine/tafamidis may cause fetal harm, product labeling recommends avoidance of pregnancy in female patients receiving tafamidis; breastfeeding is also not recommended during treatment with tafamidis. B3461091 will collect and summarize data on pregnancy outcome and birth outcome in women with ATTR exposed to tafamidis during or within 1 month prior to pregnancy.

7. RESEARCH QUESTION AND OBJECTIVES

This global, prospective, non-interventional study of women diagnosed with ATTR exposed to tafamidis during and 1 month prior to pregnancy is intended to summarize and report pregnancy and birth outcomes and potential adverse effects on the developing fetus and neonate.

The specific objectives are:

1. Describe birth outcome frequency within the reported pregnancies (live full term or premature birth, spontaneous or induced abortion, and stillbirth) in women with ATTR exposed to tafamidis during or within 1 month prior to pregnancy.

2. Describe the frequency of reported fetal, neonate and infant outcomes within the reported pregnancies (major congenital malformations/anomalies [overall and specific]), low birth weight, SGA, preterm birth, low Apgar score at 1 and 5 minutes, and infant milestone status at 6 and 12 months) following tafamidis exposure in women with ATTR during or within 1 month prior to pregnancy.

8. RESEARCH METHODS

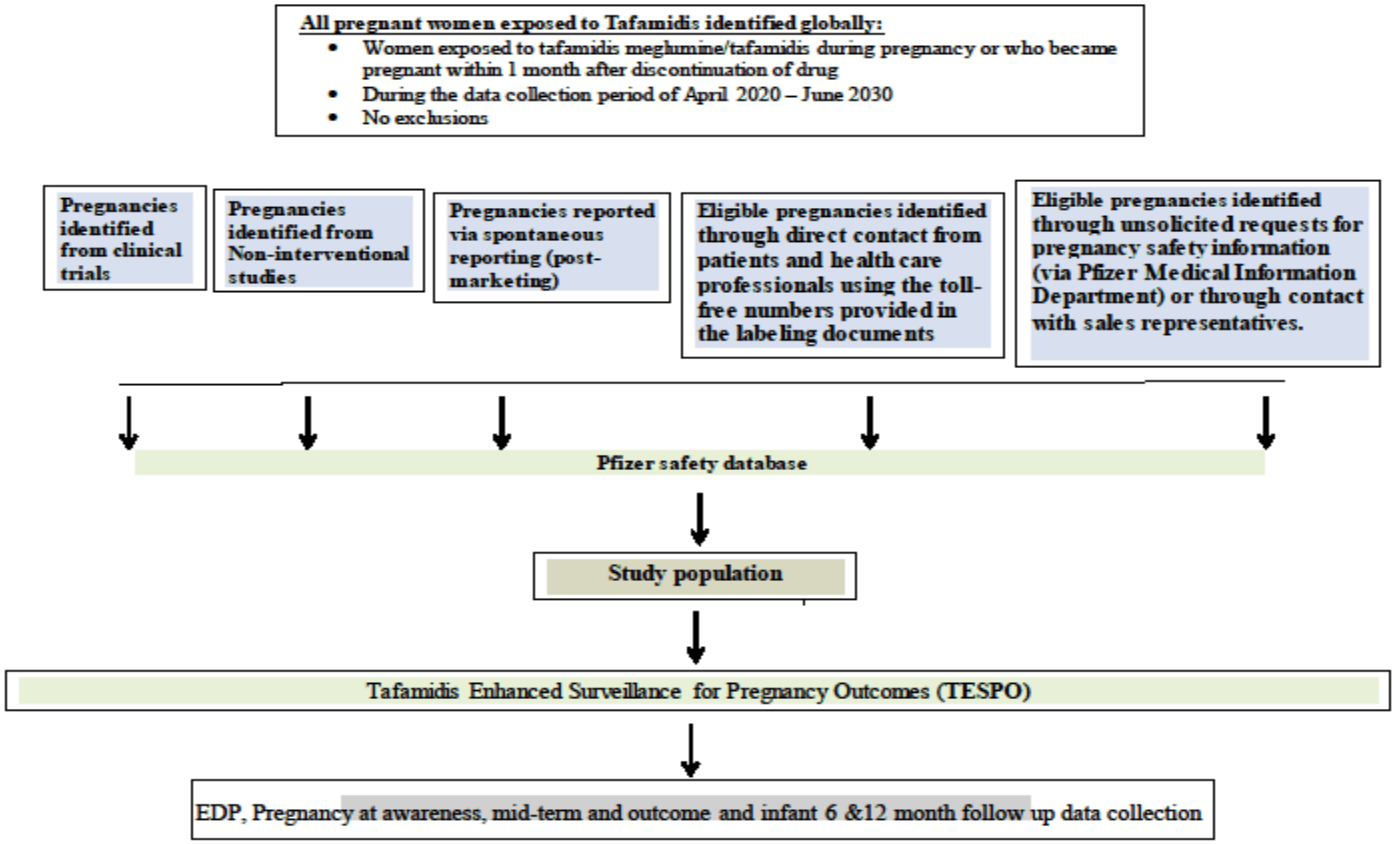
8.1. Study Design

This is a global, prospective, non-interventional study designed to collect information on pregnancy outcomes in women with ATTR exposed to tafamidis during or who became pregnant within 1 month after discontinuation of drug.

This PMR study (B3461091), which is anticipated to start in 2020 and complete in 2030 will utilize routine pharmacovigilance activities in addition to the data collection and process implemented via the ongoing Tafamdis Enhanced Surveillance for Pregnancy Outcomes (TESPO) program, which will be maintained at least until 2030. Time of enrollment is the time of initial awareness of the pregnancy reported by an investigator (clinical trial) or the HCP or patient (non-clinical source). Once initiated, all prospective pregnancy events captured via Study B3461091 (including new data collected in TESPO) will be reported to regulatory agencies in aggregate reports via Study B3461091.

TESPO is descriptive, non-interventional, observational program which has been ongoing since 2011 as an EMA post marketing requirement to assess outcome of pregnancy and birth outcomes (including major birth defects and/or developmental abnormalities in live born children up to 12 months) in female patients with ATTR-PN with exposure to tafamidis during or within 1 month prior to the pregnancy. All TESPO data are collected through use of the standard pharmacovigilance EDP form and follow-up form and the Tafamidis Enhanced Surveillance data capture aid (DCA) and 12-month follow up forms. Collection of data will be updated to include ATTR-CM. Updates will also include maternal assessment at mid-point during pregnancy and 6 month assessment of infant in addition to timepoints already collected. This collection will be achieved by adding a non-standard data collection time point (triggered at 2nd trimester of gestation) and at 6 months post delivery using the standard EDP Follow-Up Form. The data are stored in the Pfizer safety database (ARGUS) and reported with routine pharmacovigilance activities. Below is a schematic of the TESPO study design (Figure 1).

Figure 1. Study Population Flow Diagram



8.2. Setting

Events of pregnancy are reported to Pfizer:

- via clinical trials (when clinical trial participant reports pregnancy during trial);
- via non-interventional studies (eg, THAOS B3461001);
- via spontaneous reporting (post-marketing);
- through direct contact from patients and health care professionals;
- through unsolicited requests for pregnancy safety information (via Pfizer Medical Information Department);
- through contact with sales representatives.

Both maternal and paternal exposure to tafamidis were historically captured in TESPO, however, since initiation of this program it has been determined in nonclinical studies that the risk for male-mediated developmental toxicity is considered low. Consequently, exposure during pregnancy due to paternal exposure will not be required to be captured in Study B3461091.

For EDP cases occurring during sponsored clinical trials investigators are trained on how to report the case to the Sponsor, using standard PV forms.

For all other reportings, information regarding how to contact the Sponsor (per country specific labeling guidelines) in the event of a known pregnancy exposure is provided in the SmPC, the USPI, the PIL, and in informational materials provided (eg, scientific meetings and direct communication) to HCPs.

8.2.1. Inclusion Criteria

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

All women diagnosed with ATTR exposed to tafamidis during or within 1 month prior to pregnancy, reported as exposure during pregnancy (EDP) events in interventional or non-interventional clinical studies in the tafamidis development program, via spontaneous reports, solicited cases or compassionate use reports, will be included in study B3461091.

8.2.2. Exclusion Criteria

There are no exclusion criteria for this study.

8.3. Variables

Variables to be evaluated in this study include patient medical/obstetrical history and pregnancy status and outcomes, neonate and infant development status at birth, and at 6 and 12 months of age.

Variable	Description	Data Source
Maternal status		
Obstetrical History Number of pregnancies Outcome of previous pregnancies	Number of pregnancies including current pregnancy Outcomes of previous pregnancies (full term/premature live birth, stillbirth, etc) Number of living children, children born with congenital anomalies History of infertility	EDP form
Date of first day of last menstrual period	DD-MMM-YYYY	EDP form
Estimated date of conception	DD-MMM-YYYY	EDP form
Tafamidis Exposure	Formulation and dosage. Start and stop dates of tafamidis	EDP form
Exposure to concomitant medications that have risk of congenital abnormalities	Dose and start and stop dates of these concomitant medications	EDP form
Gestational age at exposure	Gestational age of fetus at exposure to tafamidis or other medication (weeks or trimester)	EDP form

Variable	Description	Data Source
Medical History Risk Factors	Risk factors for adverse pregnancy outcomes (ie, environmental exposures, eg, hypertension, diabetes, etc. Family history of congenital abnormality/genetic diseases	EDP form
Smoking	Type and number per day	EDP form
Alcohol use	Type and frequency	EDP form
Illicit drug use	Type and frequency	EDP form
Current Pregnancy		
Maternal assessment at time of study enrollment	Vital Signs BP, temp, pulse	
Smoking during pregnancy	Type and number per day	EDP form
Alcohol use during pregnancy	Type and frequency	EDP form
Illicit drug use during pregnancy	Type and frequency	EDP form
Other relevant medical conditions, use of concomitant medications, other exposures to drugs	Comorbities/hospitalizations during pregnancy/other concomitant medications or treatments taken during pregnancy	EDP form
Maternal assessment during 2nd trimester	Vital Signs BP, temp, pulse	EDP form

Variable	Description	Data Source
Smoking during pregnancy	Type and number per day	EDP form
Alcohol use during pregnancy	Type and frequency	EDP form
Other relevant medical conditions, use of concomitant medications, other exposures to drugs	Comorbities/hospitalizations during pregnancy/other concomitant medications or treatments taken during pregnancy	EDP form
Maternal assessment at delivery		
Smoking during pregnancy	Type and number per day	EDP form
Alcohol use during pregnancy	Type and frequency	EDP form
Other relevant medical conditions, use of concomitant medications, other exposures to drugs	Comorbities/hospitalizations during pregnancy/other concomitant medications or treatments taken during pregnancy	EDP form
Child status		
Neonate health status at birth	Gender, head circumference, length (cm or in), birth weight (kg or lbs) Survival, any congenital anomalies diagnosed,	EDP form

Variable	Description	Data Source
	(chromosomal testing results if performed), any medical conditions diagnosed/treated	
Neonate developmental status	Age-appropriate developmental milestones achieved or delayed	EDP form
Infant exposure during breast-feeding	Length of exposure, any interruptions in exposure	Tafamidis enhanced surveillance follow up form
Infant health status at 6 months	Survival, any congenital anomalies diagnosed, (chromosomal testing results if performed), any medical conditions diagnosed/treated Weight (kg or lbs), length (cm or in), Hospitalizations during the first 6 months	Revised form
Infant developmental status at 6 months	Age-appropriate developmental milestones achieved or delayed	Revised form
Child status at 12 months		
Health status at 12 months	Survival, any congenital anomalies diagnosed, (chromosomal testing results if performed), any	Tafamidis enhanced surveillance

Variable	Description	Data Source
	medical conditions diagnosed/treated Weight (kg or lbs), length (cm or in), Hospitalizations during the first year	follow up form
Developmental status of infant at 12 months	Age-appropriate developmental milestones achieved or delayed	Tafamidis enhanced surveillance follow up form
Medication/vaccination status at 12 months	Medications taken during the first year, vaccinations received	Tafamidis enhanced surveillance follow up form

8.4. Data Sources

The data source for this study is what is maintained in the Pfizer safety database, ARGUS (standard pharmacovigilance forms for clinical studies and the data collection forms used in the TESPO surveillance program), and described in Section 8.2.

8.5. Study Size

Sample size calculations are not applicable. All pregnant women diagnosed with ATTR meeting the inclusion criteria presented in Section 8.2.1 will be included in this study.

8.6. Data Management

8.6.1. Case Report Forms (CRFs)/Data Collection Tools (DCTs)/Electronic Data Record Process for Enhanced Surveillance

As used in this protocol, the term CRF[/DCT] should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study. For this study the data collection forms are considered the CRF.

Reported neonate and infant adverse events associated to EDPs in women exposed to tafamidis will be entered by the Pfizer Data Safety Unit (DSU) as a separate adverse event from the EDP case (cases will be linked) in the safety database. These infant adverse event cases will then be followed-up via the standard process (Table 2) used for all safety reports in order to obtain all available information. This process applies to both clinical and spontaneous EDP reports.

Table 2. Timelines for Follow-Up Requests and Additional Follow-up Attempts

Case Type	1st Follow-Up Attempt	2nd Follow-Up Attempt	Minimum Requirements
Clinical Studies	Within 10 calendar days for SRD[1]	20 calendar days after 1st f/u[2] attempt	For Pfizer-sponsored clinical studies: 2 f/u attempts and: • If contact with site is established, continue until all f/u information is obtained. • If no response from site after 2 attempts, escalate with standard "Follow-up Escalation Notice" to obtain information. For non-Pfizer-sponsored clinical studies: 2 f/u attempts and case closed as per standard Pfizer DSU[3] procedure.
Non-Clinical Sources:	Within 10 calendar days for SRD	20 calendar days after 1st f/u attempt	Two follow-up attempts and case closed as per standard Pfizer DSU procedure.

[1]: SRD: Safety Receipt Date; [2]: f/u: follow-up; [3]: DSU: Drug Safety Unit.
Source: Pfizer internal Standard Operating Procedures.

For clinical EDP cases with associated neonate and infant adverse events, the investigator is responsible for securing patient consent and collecting detailed information. For post-marketing cases the patient reporting the infant adverse event, and the patient HCP if consented by the patient, will be responsible for providing detailed information. Data on infant adverse events may be collected via three avenues: the EDP Follow-Up Form, the TESPO Form and the separate infant case process.

The revised TESPO Form Question 7 captures if major congenital anomaly(ies) has/have been confirmed by a physician. The standard EDP Follow-Up form documents congenital malformation/anomalies at birth and "diagnosed" anomalies for the neonate or infant (implies physician diagnosis).

All reports of exposure during pregnancy will be captured per regulatory and Sponsor policy in the pharmacovigilance database.

In addition to routine pharmacovigilance surveillance for women with ATTR exposed to tafamidis, additional data on pregnancy and outcome and infant status at birth, 6 and 12 month post-delivery will be collected via the data collection forms used in TESPO. In TESPO, all reported cases of tafamidis EDP and pregnancy outcomes including spontaneous abortion, birth defects and other adverse pregnancy outcomes or developmental deficits in infants will be captured in the Pfizer safety database and coded according to the current version of Medical dictionary for regulatory activities (MedDRA).

A data capture aid and/or standard Serious Adverse Event (SAE) and follow-up form will be completed for each included patient. The completed forms are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The reporter shall ensure that the forms are securely stored at the site (or equivalent) in a secured location to prevent access by unauthorized third parties.

Pfizer Clinical Study Serious Adverse Event Report

If a woman with ATTR taking tafamidis in a Pfizer-sponsored clinical study becomes pregnant, a clinical trial (CT) SAE Report Form will be completed by the Investigator, as stated in the study protocol. When the SAE report is received by the local Pfizer DSU, the local Pfizer DSU staff enters the information contained in the CT SAE Report Form into Pfizer's global safety database (ARGUS) and follows up with the investigator per standard follow–up practices for missing/discrepant/clarifying information on the CT SAE Report Form. The investigator addresses DSU queries for clarifying the initial SAE report and will use the CT Follow-up Form.

Serious Adverse Event Exposure During Pregnancy Supplemental Report (EDP) Form

This form is to be completed for all reported exposures during pregnancy, regardless of source of report. Upon receipt of information concerning an exposure to tafamidis of a woman during or within 1 month prior to pregnancy, or a reported pregnancy occurring within one month of tafamidis discontinuation, the reporter will complete a standard EDP form. This form is to be submitted to the local Pfizer DSU. If the initial contact is not an obstetric HCP, women will be requested to sign and send a release form to the reporter, which authorizes the Sponsor to contact the obstetric HCP for additional information. When the EDP report is received by the local Pfizer DSU, the local Pfizer DSU staff enters the information contained in the EDP Form into Pfizer's global safety database (ARGUS) and follows up with the investigator per standard follow–up practices for missing/discrepant/clarifying information. The investigator addresses DSU queries for clarifying the initial EDP report and will complete the query form or an additional EDP form.

The initial completed form will collect basic demographic information, medical and obstetrical history (for patient and family), pregnancy information including estimated due date and dates of all drug exposures within 1 month of pregnancy.

At the midpoint of the pregnancy and the estimated time of delivery, the obstetric HCP will be asked to complete an additional standard EDP form with reference to the status and outcome of the pregnancy. The local Pfizer DSU staff enters the information contained in the EDP Form into Pfizer's global safety database (ie, Argus) and follows up with the HCP per standard follow–up practices for missing/discrepant/clarifying information. The HCP addresses DSU queries for clarifying the follow up EDP report and will complete the query form or an additional EDP form. This form will be submitted to the local Pfizer DSU by fax (or email, if approved by Pfizer).

Tafamidis Enhanced Surveillance for Pregnancy Outcomes (TESPO) 6 and 12-Month Infant Follow-up

In the event of a live birth, the obstetric HCP will be sent a release form to be signed by the female individual to allow the Sponsor to contact the infant's pediatric HCP for additional infant outcome data. The Sponsor will contact the pediatric HCP to complete the TESPO Infant 6 and 12-Month Follow-up Form by phone or fax.

If anomalies are noted on the EDP Form or the TESPO Infant Follow-up Forms, a more detailed investigation may be initiated by the Sponsor.

Centers for Disease Control (CDC) - Measures of birth and pregnancy outcomes[24]

Measures of pregnancy and birth outcomes	Common abbreviation	Definition
Preterm birth	PTB	Birth at less than 37 completed weeks of gestation
Very preterm birth	VPTB	Birth at less than 32 completed weeks of gestation
Low birth weight	LBW	Weighing less than 2,500 grams (~5.5 pounds) at delivery
Very low birth weight	VLBW	Weighing less than 1,500 grams (~3.3 pounds) at delivery
Infant mortality	IM	Death of a live-born infant before the first birthday
Fetal death (stillbirth)	FD	Death of a fetus after the 20th week of gestation
Spontaneous fetal losses	SFL	Recognized pregnancies that do not result in induced abortions or live births; includes miscarriages, ectopic (tubal) pregnancies, and FD

Definitions for PTB, VPTB, LBW, VLBW from Martin JA, et al. 2009.[25]
Definition of IM & FD CDC. MMWR 2004.[26]
Definition of SFL from Ventura SJ, et al. 2004.[27]

According to the CDC congenital anomalies comprise a wide range of abnormalities of body structure or function that are present at birth and are of prenatal origin. For efficiency and practicality, the focus is commonly on *major* structural anomalies. These are defined as structural changes that have significant medical, social or cosmetic consequences for the affected individual, and typically require medical intervention. Examples include cleft lip and spina bifida. Major structural anomalies are the conditions that account for most of the deaths, morbidity and disability related to congenital anomalies. In contrast, minor congenital anomalies, although more prevalent among the population, are structural changes

that pose no significant health problem in the neonatal period and tend to have limited social or cosmetic consequences for the affected individual. Examples include single palmar crease and clinodactyly.

Spontaneous Reports of Pregnancy Exposure

Data contained in spontaneous sources and other data sources may be collected from patients, health care providers, lawyers, health authorities, other companies, the medical literature, and other sources, within the conduct of a NI Other Primary Data Collection Study spontaneous report or a report from other data sources. Data can be collected for a spontaneous report using the NIS Serious Adverse Event Report Form. This form is to be faxed to the local DSU and this data will be entered by the DSU into ARGUS and follow up will be performed per standard follow–up practices.

8.7. Data Analysis

Given the expected low number of reported pregnancy exposures, no formal data analysis or hypothesis testing will be conducted. Data collected on exposures and outcomes will be summarized descriptively. Summaries of the numbers of pregnancies and incidence proportion (percent) of adverse pregnancy and birth events reported via TESPO and/or captured in the standard EDP or SAE form entered into ARGUS will be provided. Women with ATTR exposed during pregnancy to concomitant medications with a known increased risk for congenital anomalies will be excluded from the descriptive summary but will be included in the study and described separately.

There are no known epidemiologic data on the incidence of adverse pregnancy outcomes in the ATTR population. Therefore, epidemiologic data on the incidence of adverse pregnancy outcomes in other populations (eg, the general population, particularly in those regions where tafamidis is commercially available and tafamidis unexposed pregnancies reported in THAOS) may be used to contextualize the findings.

A separate descriptive summary based on prospective and retrospective cases will be performed and submitted to the Agency. Prospective cases are defined as women who enroll prior to the occurrence of the pregnancy outcome (live birth, miscarriage, stillbirth, pregnancy termination). Retrospective cases are defined as women who enroll or contact the registry after the pregnancy outcome has occurred (live birth, miscarriage, stillbirth, pregnancy termination). Stratified analysis of the reported pregnancy outcomes, including pregnancies in women reported prior to start of this protocol, will be performed by daily maternal dose.

8.8. Quality Control

The data for this program will be collected using the forms provided and submitted to the Pfizer Safety Surveillance and Risk Management Department through the DSU. Review by the DSU will be performed according to their standard SOPs.

8.9. Limitations of the Research Methods

This study has three major limitations:

1. ATTR is a rare disease therefore there is a small number of patients who are diagnosed with the disease and an even smaller number of female patients who become pregnant following exposure to tafamidis. The mean age of the ATTR-PN and ATTR-CM populations are 45 and 75 years old, respectively. Because a small number of pregnancies reported is anticipated, it may limit the interpretability of the study results.

2. it is possible to have some incomplete or missing data as there is reliance on the HCP or the pregnant patient to agree to report pregnancy cases and infant follow up to Pfizer.

3. not all pregnancy exposure of women with ATTR are being reported.

Every effort will be made to obtain all data elements for reported cases and to increase the awareness of this surveillance program to elicit reporting.

8.10. Other Aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information

This study involves data that exist in anonymized structured format and contain no patient personal information. All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data on any sponsor forms, reports, publications, or in any other disclosures, except where required by applicable laws.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, subject names will be removed.

9.2. Patient Consent

The information used in this study is anonymized (ie, the information per se does not identify any patient and cannot be used to re-identify the patients with the available information) before the study is conducted. Therefore, no study-specific consent form is required for this study. However, women participating in TESPO or in sponsored clinical trials will be asked to provide agreement for a release of information from their obstetric and pediatric healthcare provider(s).

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

The IRB/EC review or approval is not required for this study.

9.4. Ethical Conduct of the Study

The study will be conducted in accordance with global and/or local legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment FDA Guidance for Industry March 2005.

9.5. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, study records must be kept for a minimum of 15 years after completion or discontinuation of the study, or longer if required by applicable local regulations.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

As noted in Section 8.2, events of pregnancy will be reported for women with ATTR receiving tafamidis via interventional and non-interventional clinical trials, via spontaneous reporting, through direct contact from patients and health care professionals using the toll-free numbers provided in the labeling documents, through unsolicited requests for pregnancy safety information (via Pfizer Medical Information Department) or through contact with sales representatives.

Regulatory reporting of adverse events/adverse reactions based on data source will occur per standard practice. Pregnancy events described in this study will have met regulatory reporting requirements as applicable based on their initial source (ie, SAE reporting of clinical trials, SAE/AE reporting of NI studies, compassionate use or spontaneous reporting).

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Descriptive data from this pregnancy surveillance study will be included in reports according to country/region specific requirements (eg, in periodic safety update reports [PSURs] in EU) at the frequency required by individual country/region regulatory requirements. Among women with ATTR who received tafamidis, these reports will provide of the numbers of adverse pregnancy events and pregnancies reported to TESPO and/or captured in the Pfizer safety database (ARGUS). Information from the study will be communicated to the scientific and medical community through relevant professional association meetings and/or a journal submission. Annual interim reports and the final study report will be submitted to the FDA according to committed timelines (Interim Report: Annually from April 2021 to April 2030; Final Report: December 2030).

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data from the participant is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

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13. LIST OF TABLES

None.

14. LIST OF FIGURES

None.

ANNEX 1. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Tafamidis Pregnancy Surveillance Study

EU PAS Register® number:
Study reference number (if applicable): B3461091

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	5
1.1.2 End of data collection[2]	☒	☐	☐	5
1.1.3 Progress report(s)	☒	☐	☐	5
1.1.4 Interim report(s)	☒	☐	☐	5

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	5
1.1.6 Final report of study results.	☒	☐	☐	5

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7
2.1.1 Why the study is conducted? (eg, to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue).	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	7
2.1.3 The target population? (ie, population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no a priori hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (eg, cohort, case-control, cross-sectional, other design).	☒	☐	☐	8.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.4
3.3 Does the protocol specify measures of occurrence? (eg, rate, risk, prevalence).	☐	☒	☐	
3.4 Does the protocol specify measure(s) of association? (eg, risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH)).	☐	☒	☐	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (eg, adverse events that will not be collected in case of primary data collection).	☒	☐	☐	10

Comments:

Section 4: Source and study populations		Yes	No	N/A	Section Number
4.1	Is the source population described?	☒	☐	☐	8.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period.	☒	☐	☐	8.1
	4.2.2 Age and sex.	☒	☐	☐	8.2
	4.2.3 Country of origin.	☐	☒	☐	
	4.2.4 Disease/indication.	☒	☐	☐	6.1
	4.2.5 Duration of follow-up.	☒	☐	☐	8.1
4.3	Does the protocol define how the study population will be sampled from the source population? (eg, event or inclusion/exclusion criteria).	☒	☐	☐	8.2

Comments:

Section 5: Exposure definition and measurement		Yes	No	N/A	Section Number
5.1	Does the protocol describe how the study exposure is defined and measured? (eg, operational details for defining and categorising exposure, measurement of dose and duration of drug exposure).	☒	☐	☐	8.7
5.2	Does the protocol address the validity of the exposure measurement? (eg, precision, accuracy, use of validation sub-study).	☐	☒	☐	
5.3	Is exposure categorised according to time windows?	☐	☒	☐	
5.4	Is intensity of exposure addressed? (eg, dose, duration).	☐	☒	☐	
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☒	☐	

Comments:

Section 6: Outcome definition and measurement		Yes	No	N/A	Section Number
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.7
6.3	Does the protocol address the validity of outcome measurement? (eg, precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study).	☐	☒	☐	

Section 6: Outcome definition and measurement		Yes	No	N/A	Section Number
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (eg, HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management).	☐	☒	☐	

Comments:

Section 7: Bias		Yes	No	N/A	Section Number
7.1	Does the protocol address ways to measure confounding? (eg, confounding by indication).	☐	☐	☒	
7.2	Does the protocol address selection bias? (eg, healthy user/adherer bias).	☐	☐	☒	
7.3	Does the protocol address information bias? (eg, misclassification of exposure and outcomes, time-related bias).	☐	☒	☐	

Comments:

Section 8: Effect measure modification		Yes	No	N/A	Section Number
8.1	Does the protocol address effect modifiers? (eg, collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect).	☐	☐	☒	

Comments:

Section 9: Data sources		Yes	No	N/A	Section Number
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (eg, pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview).	☒	☐	☐	8.4
	9.1.2 Outcomes? (eg, clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics).	☒	☐	☐	8.4
	9.1.3 Covariates and other characteristics?	☐	☒	☐	
9.2	Does the protocol describe the information available from the data source(s) on:				

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
	9.2.1 Exposure? (eg, date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber).	☐	☐	☒	
	9.2.2 Outcomes? (eg, date of occurrence, multiple event, severity measures related to event).	☒	☐	☐	8.3
	9.2.3 Covariates and other characteristics? (eg, age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle).	☒	☐	☐	8.3
9.3	Is a coding system described for:				
	9.3.1 Exposure? (eg, WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System).	☐	☒	☐	
	9.3.2 Outcomes? (eg, International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA)).	☒	☐	☐	10
	9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4	Is a linkage method between data sources described? (eg, based on a unique identifier or other).	☒	☐	☐	9

Comments:

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.7
10.2	Is study size and/or statistical precision estimated?	☐	☐	☒	
10.3	Are descriptive analyses included?	☒	☐	☐	8.7
10.4	Are stratified analyses included?	☐	☐	☒	
10.5	Does the plan describe methods for analytic control of confounding?	☐	☒	☐	
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7	Does the plan describe methods for handling missing data?	☐	☒	☐	
10.8	Are relevant sensitivity analyses described?	☐	☒	☐	

Comments:

Section 11: Data management and quality control		**Yes**	**No**	**N/A**	**Section Number**
11.1	Does the protocol provide information on data storage? (eg, software and IT environment, database maintenance and anti-fraud protection, archiving).	☒	☐	☐	8.6.1
11.2	Are methods of quality assurance described?	☒	☐	☐	8.8
11.3	Is there a system in place for independent review of study results?	☒	☐	☐	11

Comments:

Section 12: Limitations		**Yes**	**No**	**N/A**	**Section Number**
12.1	Does the protocol discuss the impact on the study results of:				
	12.1.1 Selection bias?	☐	☒	☐	
	12.1.2 Information bias?	☒	☐	☐	8.9
	12.1.3 Residual/unmeasured confounding? (eg, anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☒	☐	
12.2	Does the protocol discuss study feasibility? (eg, study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates).	☐	☒	☐	

Comments:

Section 13: Ethical/data protection issues		**Yes**	**No**	**N/A**	**Section Number**
13.1	Have requirements of Ethics Committee/Institutional Review Board been described?	☒	☐	☐	9.3
13.2	Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	9.4
13.3	Have data protection requirements been described?	☒	☐	☐	9.1

Comments:

Section 14: Amendments and deviations		**Yes**	**No**	**N/A**	**Section Number**
14.1	Does the protocol include a section to document amendments and deviations?	☒	☐	☐	4

Comments:

Deviation not discussed.

Section 15: Plans for communication of study results		**Yes**	**No**	**N/A**	**Section Number**
15.1	Are plans described for communicating study results (eg, to regulatory authorities)?	☒	☐	☐	11
15.2	Are plans described for disseminating study results externally, including publication?	☒	☐	☐	11

Comments:

Name of the main author of the protocol: Alison Flynn

Date: dd/Month/year

Signature: