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The **Ep**lontersen **Pr**egnancy and Lactation **O**utcomes Study (EPPRO): A Descriptive Safety Study of Pregnant and Lactating Individuals and Their Offspring Exposed to Eplontersen

Approved by:

PROTOCOL INFORMATION

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Research question and objectives	The objective of this descriptive pregnancy safety study is to describe the prevalence of pregnancy and maternal complications and adverse effects on the developing fetus, neonate, and infant among individuals exposed to eplontersen during pregnancy and/or lactation.

Country (-ies) of study	Global
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2. LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACOG	American College of Obstetricians and Gynecologists
ADR	Adverse drug reaction
AE	Adverse Event
ART	Assisted reproductive technology
ATTR	Transthyretin amyloidosis
ATTR-CM	Transthyretin amyloidosis with cardiomyopathy
ATTR-PN	Transthyretin amyloidosis with polyneuropathy
AZ	AstraZeneca
CI	Confidence interval
DOC	Date of conception
DPSS	Descriptive Pregnancy Safety Study
EDD	Estimated date of delivery
EOP	End of pregnancy
EPPRO	Eplontersen Pregnancy and Lactation Outcomes Study
FDA	Food and Drug Administration
hATTR	Hereditary transthyretin amyloidosis
hATTR-PN	Hereditary transthyretin amyloidosis with polyneuropathy
HCP	Healthcare provider
ICSR	Individual Case Safety Report
KUR	Keep Under Review
LMP	Last menstrual period
MACDP	Metropolitan Atlanta Congenital Defects Program
MCM	Major congenital malformation
NOS	Not otherwise specified
PRIM	Pregnancy outcomes intensive monitoring
PV	Pharmacovigilance
PV-Argus	Pharmacovigilance Global Safety database
SAB	Spontaneous abortion
SGA	Small for gestational age
SOP	Standard operating procedure
TSQ	Targeted safety questionnaire
TTR	Transthyretin

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Abbreviations: AZ = AstraZeneca; PPD = Pharmaceutical Product Development, LLC; UK = United Kingdom; USA = United States

4. ABSTRACT

Title

The Eplontersen Pregnancy and Lactation Outcomes Study (EPPRO), A Descriptive Safety Study of Pregnant and Lactating Individuals and Their Offspring Exposed to Eplontersen

Version 3.0 / 04 February 2026

Authors: Myriam Alexander, PhD, MPhil, AstraZeneca; Alice Rouleau, PharmD, MScPH; PPD, part of Thermo Fisher Scientific; Yassaman Vafai, PhD, MPH; PPD, part of Thermo Fisher Scientific

Rationale and background

Currently, there are no clinical studies of eplontersen use in pregnant individuals. Although it is expected that exposure to eplontersen during pregnancy or lactation is very rare, it is important to capture as many exposed cases as possible. This descriptive pregnancy safety study (DPSS) will add to the current body of knowledge regarding the safety of eplontersen exposure during pregnancy and lactation and maternal, fetal, and infant outcomes following exposure to eplontersen. The study is designed to fulfill health authorities' post-marketing requirements.

Research question and objectives

The overall objective of this DPSS is to describe the occurrence of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant associated with exposure to eplontersen during pregnancy and/or lactation.

Study design

This DPSS will analyze secondary data on cases of eplontersen-exposed pregnant and lactating individuals collected through a PRegnancy outcomes Intensive Monitoring (PRIM) enhanced pharmacovigilance (PV) approach utilizing AstraZeneca's PV Global Safety Database (PV-Argus).

Population

All PV reports of individuals with a diagnosis that is an approved indication for the use of eplontersen and who were exposed to at least one dose of eplontersen during pregnancy and/or lactation.

Variables

Exposure to eplontersen is a criterion for inclusion in the DPSS. Individuals will be considered exposed if at least one dose of eplontersen is administered at any time during pregnancy from 15 weeks (105 days) before date of conception (DOC) until the end of pregnancy (EOP), when a DOC can be determined. In cases of missing DOC, the last menstrual period will be used. Individuals will be considered exposed during lactation if at least one dose of eplontersen is administered at any time during lactation up to 12 months post-pregnancy. Infant outcomes will be collected up until 1 year of age. However, if there is ongoing exposure to eplontersen and continuation of breastfeeding at 260 days (approximately 8 months) post-pregnancy or later, the follow-up period will be extended an additional 15 weeks to EOP+470 days.

The outcomes of interest include a composite outcome of all major congenital malformations, a composite outcome of all minor congenital malformations, pregnancy complications, spontaneous abortion, stillbirth, induced abortion, preterm birth, small for gestational age, postnatal growth deficiencies, infant development delay, neonatal mortality, infant mortality, as well as any other infant adverse events.

Data sources

All eplontersen-exposed cases reported to AstraZeneca PV-Argus as notifiable events related to pregnancy and lactation; and cases reported from clinical trials, spontaneous post-marketing reports, post-marketing observational studies, patient-oriented programs, published literature, and personal communication by healthcare providers will be eligible for inclusion in the analysis. Data on eplontersen-exposed cases will be captured and processed using a pre-specified follow-up schedule and questionnaires. In case of missing data, there will be several attempts to collect data using all contact methods supplied by the reporters at the time of initial report.

Study size

This DPSS is descriptive in nature, and a formal sample size calculation is not performed. Feasibility calculations indicate that the DPSS may capture five exposed pregnancies over the study period.

Data analysis

Analyses will be conducted in accordance with the study objectives, table/listing shells, and applicable guidelines. Demographics, medical and obstetric history, and disease characteristics will be summarized using descriptive statistics. The outcomes will be reported as a proportion and 95% confidence interval (if applicable) and calculated by dividing the number of cases of the outcome by the appropriate denominator for the particular outcome. If

fewer than ten cases are reported, formal analyses will not be performed, and reporting will be limited to case narratives.

Milestones

Following submission to health authorities and approval of the protocol, the study will be launched. Data collection is expected to started in Q4 2025 and planned to continue for 10 years. Interim analyses will be submitted starting in November 2026 and annually thereafter. A final report will be submitted to the corresponding health authorities at the conclusion of the study.

5. AMENDMENTS AND UPDATES

Table 1 Substantial amendments and updates

Version Identifier	Date	Protocol Section Changed	Summary of Amendment	Reason
V3.0	04 February 2026	4, 9.3.2, Figure 1	Revised the exposure period to 15 weeks before DOC until the EOP, when a DOC can be determined	FDA comment
V2.0	20 June 2025	3	Revised responsible parties	Change in AZ and PPD staff
V2.0	20 June 2025	4; 9.1; 9.2; 9.4	Added published literature and personal communication by HCPs as the sources of eplontersen-exposed cases	FDA comment 1
V2.0	20 June 2025	2; 4; 9.3; Figure 1	Revised definition of the exposure period anchoring it to DOC and added clarification related to using LMP when DOC could not be determined. Added explanation on determining gestational weeks for further clarification	FDA comment 2
V2.0	20 June 2025	9.3.5; Table 7; Table 8	Added clarification on the collection of type of reporter (pregnant individual vs HCP) and their contact information for reporter including telephone number, address, and email address as well as dates initial report and any follow-up contact	FDA Comment 3
V2.0	20 June 2025	8; Table 5	Added details to the data collection related to assessment of infant developmental delays during the follow-up period from end of the pregnancy	FDA comment 3
V2.0	20 June 2025	9.1; 9.6; Table 7	Added an additional administration of the targeted safety questionnaire at 24 weeks gestation for pregnancies initially reported before 20 weeks of gestation	FDA comment 4

Abbreviations: AZ = AstraZeneca; DOC = date of conception; EOP: end of pregnancy; FDA = Food and Drug Administration; HCP = healthcare provider; LMP = last menstrual period; PPD = Pharmaceutical Product Development, LLC

6. MILESTONES

Table 2 Study milestones

Milestone	Planned date
Start of data collection (planned)	30 November 2025
Interim report 1	30 November 2026
Interim report 2	30 November 2027
Interim report 3	30 November 2028
Interim report 4	30 November 2029
Interim report 5	30 November 2030
Interim report 6	30 November 2031
Interim report 7	30 November 2032
Interim report 8	30 November 2033
Interim report 9	30 November 2034
Interim report 10	30 November 2035
End of data collection	30 December 2035
Final report of study results	30 December 2036

7. RATIONALE AND BACKGROUND

7.1 Hereditary transthyretin amyloidosis with polyneuropathy

Hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN or ATTRv-PN) is a rare, progressive, autosomal dominant disease manifested through sensorimotor and autonomic neuropathy symptoms (1). hATTR-PN is caused by extracellular accumulation of misfolded mutated transthyretin (TTR) protein fibrils, predominantly in the peripheral nerves (2, 3). In patients with hATTR-PN, misfolded TTR proteins accumulate in multiple systems, including the heart, gastrointestinal tract, and other organs, with great variability in clinical presentation and course, leading to death within 10 years, on average (4).

Epidemiologic data on the occurrence of hATTR-PN are scarce. In Europe, the incidence of ATTRv-PN is estimated at 0.3 to 10 cases per 1,000,000 per year (between 5,000 and 6,000 patients) (5). Data from the ATTReuNET questionnaire suggest that Portugal has the highest number of diagnosed symptomatic cases of ATTRv-PN (2,000 cases) and more than 500 diagnosed asymptomatic carriers of the disease (6, 7).

Globally, prevalence is reported at approximately 50,000 individuals for hATTR (8), and 10,000 individuals for hATTR-PN (9) with a slightly higher proportion of men than women experiencing hATTR-PN (59% vs 41%) (7). In Europe, the overall prevalence of ATTRv is

estimated at less than 10 in 1,000,000 individuals (10). Areas of endemicity of ATTRv have been reported in Cyprus, with an estimated prevalence in 2016 of 54 per 1,000,000 individuals (11).

In endemic countries such as Brazil and Portugal, hATTR-PN is mostly diagnosed in the third to fifth decade of life (2); in non-endemic countries, however, diagnosis is often delayed because of difficulty in recognizing the symptoms (12). In a large global case series, the earliest average age at diagnosis across all variants was 53.4 years, whereas the overall average was 64 years (12); however, both prevalence and distribution of age at diagnosis vary significantly geographically, with higher prevalence and younger ages of diagnosis in endemic areas, such as Portugal, Cyprus, Spain, France, Japan, and North Sweden and in descendants from these regions, compared with the rest of the world (6, 8).

Given the later age at symptom onset and diagnosis, most female patients will be beyond reproductive years. As such, the scientific literature on pregnancy among amyloidosis patients is limited to case reports (13-15), and no case reports of lactation among amyloidosis patients were identified via a targeted literature review. Currently, no data on the incidence or prevalence of pregnancy and lactation in the hATTR-PN population are available.

7.2 Current treatment paradigm

Management of patients with hATTR warrants a multidisciplinary approach. Although liver transplantation used to be the standard of care for patients with hATTR-PN (10), advances in pharmacotherapeutic alternatives have changed treatment recommendations to include i) targeted anti-amyloid therapy to inhibit further production and/or deposition of amyloid aggregates, ii) symptomatic therapy of sensorimotor and autonomic polyneuropathy, iii) treatment of cardiac, renal, and ocular involvement, and iv) genetic counseling of patients and relatives (1).

Targeted anti-amyloid drugs include stabilizers of the TTR tetramer (i.e., tafamidis), which prevent its dissociation into monomers and amyloidogenic and toxic intermediates, and silencers (i.e., inotersen, patisiran, and vutrisiran) which reduce or block TTR synthesis (16). Targeted anti-amyloid drugs are currently indicated in the early stages (i.e., stages 1 and 2) of hATTR-PN when the patient is ambulatory without or with some assistance, respectively (17)). For later stages, organ transplantation is still the recommended treatment (1). Concurrent use of a stabilizer and silencer for treating hATTR-PN may exist, although it is unlikely, as monotherapy by silencer has been shown to be superior to concomitant use of both classes (18). There are also limited data on treatment safety of these targeted anti-amyloid drugs during pregnancy. In 18 reported cases of maternal or paternal exposure to tafamidis during pregnancy or 1 month before pregnancy, there was one case of spontaneous abortion, one medical termination, 12 normal newborns, and three outcomes pending at the time of report (19).

Currently, four silencers are commercially available: eplontersen, inotersen, patisiran, and vutrisiran. When treated with one of these drugs, supplementation with vitamin A (a fat-soluble vitamin) is recommended because of the role TTR plays as a transporter via binding to retinol-binding protein (20). During pregnancy, vitamin A is also an essential component of normal embryofetal development; however, excessive vitamin A intake during pregnancy has been shown to exert teratogenic effects and cause adverse fetal development events—therefore, these drugs are not recommended for intake during pregnancy (21, 22). Currently, there are no data on the impact of treatment with silencers during pregnancy on the fetus, i.e., of a reduction in maternal serum TTR due to treatment compensated by vitamin A supplementation. Patients considering pregnancy while taking those medications are currently advised to consider potential risks to the fetus. Similarly, data on exposure to these drugs during lactation are lacking. In studies on lactating rats treated with patisiran, lipid components of patisiran, but not patisiran itself, were detected in milk (22). For lactation, in the absence of data, physicians are advised to perform a risk-benefit assessment before making any recommendation on the use of any of those treatments.

Eplontersen is a ligand-conjugated antisense medication approved in the USA for the treatment of ATTR with polyneuropathy (ATTR-PN), and a Phase III trial for ATTR with cardiomyopathy (ATTR-CM) is ongoing. Eplontersen was granted Orphan Drug Designation in the US by the Food and Drug Administration and in the EU by the European Commission for the treatment of ATTR in January 2022 (23, 24).

In the current label information, due to the potential teratogenic risk arising from unbalanced vitamin A levels, eplontersen is not recommended for use during pregnancy. Individuals in their reproductive age are advised to use effective contraception, and in case of pregnancy, close monitoring of the fetus and vitamin A status should be carried out, especially during the first trimester.

7.3 Knowledge gap

Eplontersen and other TTR protein silencer drugs reduce the production of TTR protein, which is a transporter of vitamin A (25). Lack or excess of vitamin A during embryonic development, in turn, may result in congenital malformations (26). Therefore, treatment with drugs such as patisiran during pregnancy is not recommended (22), and because of ethical reasons, pregnant or lactating individuals have been excluded from completed or ongoing trials on eplontersen and other similar medications. Treatment with similar medications has also been discontinued for any patient who became pregnant during the clinical trials. Consequently, there are no data on patients exposed to eplontersen or similar silencers during pregnancy or their breastfed infants; however, in animal studies of patisiran treatment during lactation, lipid components of the medication were found in the milk (22).

In nonclinical rodent studies for eplontersen, there were no measurable levels of eplontersen in the placenta or fetal liver, indicating that eplontersen is not readily absorbed by the placenta or transported to the fetus. There were also no adverse effects on embryofetal developmental, or pre- or postnatal development observed; however, no human data on such adverse effects exist. A similar medication, inotersen, produced no adverse effects on fertility and embryofetal development when studied in mice or rabbits, and no effects on pre- and postnatal development when studied in mice. Eplontersen concentrations in breast milk have not been evaluated, but the concentration of inotersen in breast milk was very low in preclinical studies and more than 600-fold lower compared with the concentrations measured in liver. As the clinical dose of eplontersen is 25 times lower than the clinical dose of inotersen, and eplontersen is an antisense oligonucleotide with expected poor oral bioavailability, concentrations of eplontersen in breast milk are likely minimal.

7.4 Study rationale

Currently, there are no clinical studies of eplontersen in pregnant or lactating individuals. As a result, there is a need for long-term (i.e., 12 months) data collection to characterize the risk of adverse maternal, fetal, and infant outcomes associated with eplontersen exposure in the real-world setting. This descriptive pregnancy safety study (DPSS) will add to the current body of knowledge regarding the safety of eplontersen exposure during pregnancy and lactation and fulfill health authorities' post-marketing requirements.

Given the epidemiologic characteristics of the disease, it is anticipated that exposure during pregnancy is likely a very rare event for the entirety of the observation period. To maximize the capture of any globally reported cases and to increase the quality and completeness of collected data, this DPSS is being executed using secondary data reported through AstraZeneca's (AZ) pharmacovigilance (PV) Global Safety Database (PV-Argus), enhanced with a PRegnancy outcomes Intensive Monitoring (PRIM) approach.

The PRIM approach harnesses the existing PV reporting system including the process for close surveillance[1] of potential risks for a medicinal product where further understanding is required. The use of a targeted safety questionnaire (TSQ) to improve data collection accuracy and completeness forms is part of the existing PV process. Therefore, PRIM is regarded a secondary data collection approach and does not require consent. A pilot study comparing the PRIM approach to a matching prospective pregnancy registry showed significantly higher rates of case capture with 184 prospective registry pregnancies compared with 725 cases captured through PRIM. (27). The recognition of the shortcomings of traditional registry-based studies recently led to the European Medicines Agency accepting a PRIM approach for

[1] Close surveillance is defined as "Performance of more extensive analysis of the information retrieved/available for a Keep Under Review (KUR) Term above and beyond that mandated for routine signal management."

the safety monitoring of fingolimod exposure during pregnancy (28, 29). Collectively, this suggests that the use of a PRIM approach for eplontersen will result in more rapid and efficient capture of exposed pregnancies and will also provide a more comprehensive risk assessment.

8. RESEARCH QUESTION AND OBJECTIVES

The aim of this DPSS is to describe the occurrence of pregnancy and maternal complications and adverse effects on the developing fetus, neonate, and infant among individuals exposed to eplontersen during pregnancy and/or lactation. The incidence of each of the outcomes of interest will be estimated among individuals exposed to at least one dose of eplontersen during pregnancy; the incidence of infant outcomes will also be assessed among infants exposed to eplontersen through breastmilk feeding.

8.1 Outcomes

Outcomes of interest are listed below. For information on the definitions of these outcomes, see Section 9.3.4.

- Composite outcome of all major congenital malformations (MCMs)
- Composite outcome of all minor congenital malformations
- Molar or ectopic pregnancy
- Gestational diabetes
- Gestational hypertension, preeclampsia, eclampsia
- Placental disorder
- Fetal loss
    - Spontaneous abortion (SAB)
    - Stillbirth
    - Induced abortion
    - Fetal loss, type not specified
- Live birth
- Preterm birth
- Small for gestational age (SGA)
- Neonatal death
- Postnatal growth deficiency
- Infant developmental delay including assessment of social/emotional, language/communication, cognitive (learning, thinking, problem-solving), and movement/physical development)
- Infant death

9. RESEARCH METHODS

9.1 Study design

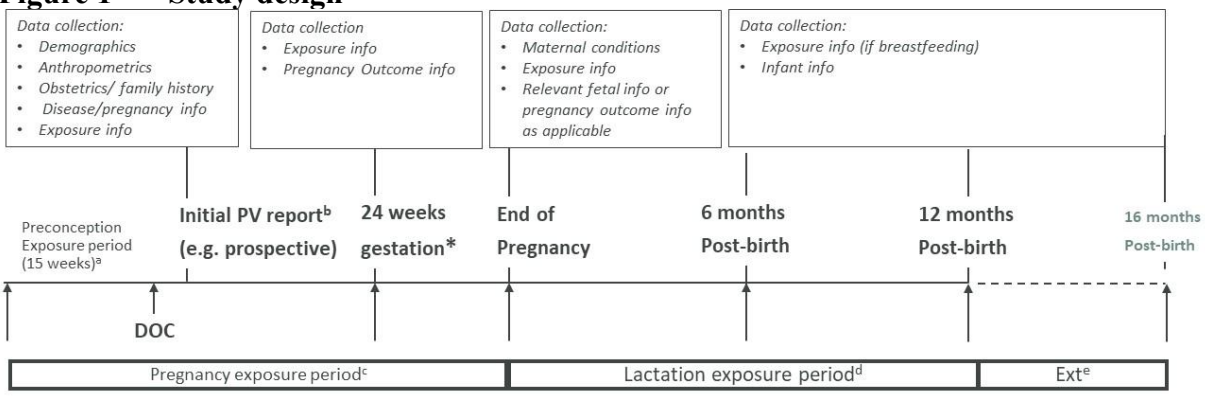
This DPSS will utilize secondary data collected through AZ PV-Argus, improved with implementation of a PRIM approach (29). The PRIM approach utilizes AZ PV-Argus and the close surveillance approach for enhanced data collection on spontaneous individual case safety reports (ICSR) of pregnancies and lactation cases considered as special reportable scenarios, and ICSRs of adverse pregnancy and/or infant outcomes reported as suspected adverse drug reaction (ADR). PRIM includes several enhancements to routine PV as suggested by Geissbühler et al. (29):

- Extended data collection
- More attempts at each data collection point
- Contacting the reporters through all possible means for patient-oriented programs if local regulations permit
- Automated check of overdue follow-up
- Data collection and follow-up on normal infants, as well as those reporting adverse events (AEs)/malformation
- Adjudication of cases of malformation (and categorization of major, minor, or other types of malformation by an external expert panel)
- Enhanced data quality control and data correction focusing on crucial data needed for programmed statistical data aggregation
- Programmed data extraction and aggregate analysis planned and mapped a-priori

The close surveillance PRIM process will apply to all eligible subjects for whom ICSRs have been submitted into the AZ PV-Argus for the study period defined by a maximum of 10 years from latest date of market authorization in each country or 1 November 2025, whichever is the latest. The source of these cases includes clinical trials, spontaneous post-marketing reports, post-marketing observational studies, patient-oriented programs, published literature and personal communication by healthcare providers (HCPs). The PRIM data will be limited to capturing the minimum information necessary for analysis and, as it is secondary data analysis, it will be restricted to the fields that are used in PV reporting. Data collection will be ongoing as data become available and evaluated on an annual basis.

An indicative study design is summarized in Figure 1. Details of exposure definitions are provided in Section 9.3.2.

Figure 1 Study design



Abbreviations: DOC: date of conception; Ext: extension; PV: pharmacovigilance. [a]Time to product elimination (5 times terminal half-life from LMP; eplontersen half-life = 3 weeks); [b]Cases may be retrospectively included into the PRIM program up to 1 year after pregnancy outcome; [c]If a case is exposed to the product during this time, they will be considered exposed during pregnancy; [d]If a case is exposed to the product while breastfeeding during this time, they will be considered exposed during lactation; [e] If eplontersen exposure and breastfeeding is ongoing at 8 months post-pregnancy or later, follow-up will be extended up to 470 days post-pregnancy. If DOC is not known, the date of last menstrual period (LMP) will be used instead of DOC to define the preconception exposure period.
*24 Weeks follow-up during pregnancy will occur for initial PV reports that are received prior to 20 gestational weeks.

The scheduling of questionnaires is as follows:

- After the initial pregnancy notification report
- At 24 weeks gestational age (±4 weeks): this will allow capturing of information related to adverse pregnancy outcomes such as spontaneous abortion (miscarriage) for pregnancies with the initial PV report prior to 20 weeks of gestation
- At end of pregnancy (EOP) defined as when pregnancy outcome occurs via live birth or fetal loss
- At EOP plus 180 days
- At EOP plus 365 days
- At EOP plus 470 days if the breastfed infant is exposed to eplontersen at 240 days post-pregnancy

Medical review and adjudication will be performed as follows leveraging AZ PV-Argus. All ICSRs, including lactation and pregnancy reports, will be handled according to the standard global case handling workflow for inclusion in AZ PV-Argus as per routine PV procedure for products which are under close surveillance as part of a Keep Under Review process (KUR). This process includes enhanced data entry, review of all incoming KUR case reports during every routine surveillance run, and cumulative review of the medical concept to be performed

at least annually. Medical review of the reports will be performed for serious adverse reactions, as per routine PV case handling procedure. Reports of eplontersen-exposed cases will then be exported into an analytical database specific to the DPSS, and analysis will be performed for the DPSS complementary to routine signal detection using AZ PV-Argus. Relevant data outside of spontaneously reported ICSRs, i.e., AE, pregnancy, or lactation reporting from clinical trials or observational studies, will also be entered into AZ PV-Argus in the same manner. Any case with a reported congenital malformation will undergo formal, independent adjudication as part of the PRIM approach enhancement as described in Section 9.3.4.1.

9.2 Setting

9.2.1 Study duration and follow-up

Following submission to health authorities and approval of the protocol, the DPSS will be launched. Exposed case collection with the PRIM approach is expected to begin in November 2025 and will conclude in December 2035, i.e., data collection is planned for approximately 10 years. For each exposed pregnancy, follow-up begins with the initial PV report and ends at pregnancy outcome (if fetal loss) or at 12 months after pregnancy outcome (if live birth). For instances where there is only lactation exposure, follow-up begins with the initial PV report and ends 12 months after birth. In cases with ongoing exposure during breastfeeding at 8 months post-pregnancy or later, the follow-up period will be extended by an additional 15 weeks to EOP+470 days.

9.2.2 Study population

The study population will include all PV reports of pregnant and/or lactating individuals diagnosed with an indication approved for use of eplontersen who administered at least one dose of eplontersen during pregnancy or lactation (see Section 9.3.2 for detailed exposure definitions). Both prospectively and retrospectively reported cases will be included in the study population as defined below in Table 3. Cases that were reported before or in the middle of the PRIM launch will also be eligible for inclusion but will be reported separately as the data collection and documentation methodology will be inherently different.

Table 3 Case classifications

Timing and results of prenatal testing	**Eplontersen PRIM case classification**
Pregnancy outcome has not occurred, and prenatal tests have not been performed at the time of initial PV report	Prospective
Prenatal testing had been performed at the time of initial PV report, but results were not yet available or received by reporter	Prospective
Prenatal test results were available and were normal at the time of initial PV report	Prospective
Prenatal test results were available and were known to be abnormal at the time of initial PV report	Retrospective
Outcome of pregnancy known at the time of initial PV report	Retrospective
Timing of data collection related to PRIM initiation	**Eplontersen PRIM case classification**
Initial report of pregnancy or lactation exposure and 12-months postpartum period prior to initiation of PRIM	Pre-PRIM
Initial report of pregnancy or lactation exposure prior to initiation of PRIM, but follow-up ongoing after initiation of PRIM	Mixed Pre/Post PRIM
Initial report of pregnancy or lactation exposure occurs after initiation of PRIM	Post-PRIM

Abbreviations: PRIM = pregnancy outcomes intensive monitoring; PV= pharmacovigilance.

Definitions of retrospective and prospective cases as per European Medicines Agency guidance (30).

9.2.3 Inclusion criteria

All pregnancy and/or lactation cases with exposure to eplontersen and a diagnosis of an approved indication reported to the AZ PV database via clinical trials, spontaneous post-marketing report sources, post-marketing observational studies, patient-oriented programs, published literature, and personal communication by HCPs are eligible for inclusion in the study. This is to include:

1. All notifiable pregnancy and lactation case reports in individuals exposed to eplontersen and diagnosed with an approved indication for treatment with eplontersen

2. All AE reports in infants in the first 12 months of age that are or can be linked to pregnancy or lactation reports in individuals previously diagnosed with an approved indication and exposed to eplontersen during pregnancy or lactation

This study will not include any eplontersen-unexposed pregnancies. At the time of protocol development, hATTR-PN is the only approved indication for eplontersen.

9.2.4 Exclusion criteria

The following case reports to the AZ Global Safety Database via clinical trials, spontaneous post-marketing report sources, post-marketing observational studies, patient-oriented programs, published literature, and personal communication by HCPs will be excluded:

1. All case reports considered invalid (i.e., minimum data are not provided at first report nor follow-up), or where reporter indicates that they do not wish to be contacted to obtain follow-up information, or the reporter/patient cannot be identified

9.3 Variables

9.3.1 Gestational week calculation

According to the American College of Obstetricians and Gynecologists (ACOG) terminology, last menstrual period (LMP) is defined as the first day of the most recent menstrual period before the individual becomes pregnant. LMP is a key date for estimating gestational age (i.e., how far the pregnancy is in weeks from LMP) and the estimated date of delivery (EDD) (i.e., estimated due date of the baby). Per, ACOG recommendation, gestational age and the EDD should be determined by the obstetric HCP as soon as data are obtained regarding the LMP, first accurate ultrasound, or both. ACOG considers ultrasound measurement of the embryo or fetus in the first trimester (up to and including $13^{6/7}$ gestational weeks) the most accurate method to establish or confirm gestational age and discourages changing the EDD based on subsequent ultrasounds. Any pregnancy without an ultrasound before $22^{0/7}$ gestational weeks to confirm or revise the EDD should be considered suboptimally dated. If the pregnancy resulted from assisted reproductive technology (ART), the obstetric HCP should use ART-derived gestational age (e.g., based on age of embryo and date of transfer) to determine EDD. ACOG further recommends that the best estimate of EDD by the obstetric HCP, rather than estimates based on LMP alone, be used for research purposes (31, 32).

Therefore, based on EDD, the following will be calculated:

- First day of LMP, defined as $0^{0/7}$ gestational week, will be calculated as EDD minus 280 days (40 weeks)
- Gestational age will be calculated as the number of weeks elapsed since the first day of LMP
    - Gestational weeks $0^{0/7}$ to $13^{6/7}$ will be considered the “first trimester”
    - Gestational weeks $14^{0/7}$ to $27^{6/7}$ will be considered the “second trimester”
    - Gestational weeks $28^{0/7}$ to pregnancy outcome will be considered the “third trimester”

LMP and EDD will be collected as part of the study follow-up questionnaire. If both LMP and EDD are reported, EDD will be used to calculate gestational week as recommended by ACOG. If EDD is not reported, but LMP data are available, LMP will be used to calculate EDD and gestational age.

9.3.2 Exposure definition

Date of conception (DOC) is generally defined as $2^{0/7}$ gestational weeks and will be collected as part of the study follow-up questionnaire. Exposure to eplontersen during pregnancy will be

defined as administration of at least one dose of eplontersen at any time during pregnancy from 15 weeks before DOC until the EOP (i.e., when pregnancy outcome occurs via live birth or fetal loss), when a DOC can be determined. The preconception exposure period of 15 weeks before DOC was chosen based on the calculation of five times the half-life of eplontersen which has been estimated as 3 weeks.

In cases where DOC cannot be determined from the available data, LMP will be used to calculate exposure. Exposure to eplontersen during pregnancy will then be defined as administration of at least one dose of eplontersen at any time during pregnancy from 15 weeks before LMP until the EOP.

Exposure to eplontersen during lactation will be defined as use of eplontersen at any time during breastfeeding from the first day of lactation initiation (expected to be the date of delivery) up through 12 months (EOP+ 365 days) post-pregnancy. Infants will be considered exposed until the last day on which the infant was breastmilk-fed, even if breastmilk feeding was done alongside other types of feeding methods such as powdered milk/formula or solid food. In the event of ongoing eplontersen exposure and breastfeeding at 8 months or later post-pregnancy, follow-up will be extended by an additional 15 weeks to EOP+470 days.

For each specific outcome, the appropriate timing of exposure to eplontersen will be considered and an “at-risk exposure” will be defined. For congenital malformations and ectopic pregnancy, only first-trimester exposures will be considered as etiologically relevant. For other outcomes, exposure throughout the pregnancy will be considered. Information related to date, frequency, duration, and dosage of eplontersen use will be collected for exposure.

9.3.3 Disease definition

The indication for use of eplontersen will be based on the recorded information given by the reporter to AZ’s PV system and will be analyzed as recorded. The date of diagnosis and severity of symptoms during pregnancy will also be recorded. Age at diagnosis will be derived. The severity of hATTR-PN will be based on the Coutinho scoring system, where stage 1 is independent ambulation, stage 2 is need for unilateral or bilateral support for ambulation, and stage 3 is wheelchair-bound or bedridden (33). If additional or alternative severity scores are available, these will also be collected.

9.3.4 Outcome definition

Maternal, pregnancy, neonatal, and infant-related outcomes of interest and definitions are listed in Table 4 and Table 5. These will be used in the calculation and analyses of the outcomes.

Table 4 Definition of maternal and pregnancy outcomes

Outcome	Definition
Maternal Outcomes	
Gestational diabetes	Any degree of glucose intolerance with onset or first recognition during pregnancy (34)
Pregnancy-induced hypertension	A disorder of pregnancy defined as a systolic blood pressure of 140 mmHg or more or a diastolic blood pressure of 90 mmHg or more, or both, on 2 occasions at least 4 hours apart after 20 weeks gestation, in a woman with previously normal blood pressure (35)
Preeclampsia	A disorder of pregnancy associated with new-onset hypertension, which occurs most often after 20 weeks of gestation and frequently near term, and proteinuria. Or, in the absence of proteinuria, it is defined as new-onset hypertension with the new onset of any of the following: • Thrombocytopenia: platelet count <100,000/mL • Renal insufficiency: serum creatinine concentrations >1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease • Impaired liver function: elevated blood concentrations of liver transaminases to twice normal concentration • Pulmonary edema New-onset headache unresponsive to medication and not accounted for by alternative diagnoses or visual symptoms (35)
Eclampsia	New-onset tonic-clonic, focal, or multifocal seizures in the absence of other causative conditions such as epilepsy, cerebral arterial ischemia and infarction, intracranial hemorrhage, or drug use (35)
Premature rupture of membrane	Rupture (breaking open) of the membranes (amniotic sac) before labor begins (36)
Placenta previa	Placenta is partially or completely covering the opening of the uterus (cervix) (37)
Placental abruption	Early separation of the placenta from the lining of the uterus before completion of the second stage of labor (38)
Incompetent cervix	Inability of the cervix to retain the fetus, in the absence of uterine contractions or labor, owing to a functional or structural defect (39)
Emergency cesarean	A cesarean delivery that is performed due an immediate threat to the health or safety of the fetus and/or the mother (40)
Maternal hospitalization for illness	Inpatient hospitalization required for any maternal illness
Maternal death	Death of a woman while pregnant or ≤42 days after the end of the pregnancy (including live/stillbirth delivery, ectopic pregnancy, miscarriage or termination) from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes (41)
Pregnancy Outcomes	
Ectopic pregnancy	Implantation of the embryo outside of the endometrial cavity (including tubal, cervical, cesarean scar, interstitial, cornual, ovarian, abdominal, heterotopic, or of unknown location) confirmed by transvaginal ultrasound
Molar pregnancy	A non-viable product of conception which can be either a “complete mole” arising after single sperm fertilization of an ovum lacking genetic material, or a “partial mole” which arises as a consequence of multi-sperm fertilization of a healthy ovum. An invasive mole (formerly known as chorioadenoma destruens) is a hydatidiform mole that has grown into the muscle layer of the uterus
Spontaneous abortion	Fetal death or the expulsion of the products of conception occurring at <20 gestational weeks (42)

Outcome	Definition
Stillbirth	A fetal death occurring at ≥20 gestational weeks or, if gestational age is unknown, a fetus weighing ≥350 g (43)
Induced abortion	An intervention that is intended to terminate a suspected or known ongoing intrauterine pregnancy and that does not result in a live birth (44)
Live birth	Delivery of a fetus, irrespective of the duration of the pregnancy, which after separation shows signs of life, such as beating of the heart, breathing, pulsation of the umbilical cord, or definite movement of voluntary muscles (41)
Preterm birth	A birth occurring at <37 gestational weeks (45)
Lost to FU	No further information is received regarding pregnancy outcome even after pursuing an appropriate number of follow-ups for a case.

Abbreviation: FU = follow-up

Table 5 Definition of neonatal/infant outcomes

Neonatal or infant outcome	Definition
Major congenital malformation	An abnormality of body structure or function that is present at birth, is of prenatal origin (i.e., birth defect), has significant medical, social, or cosmetic consequences for the affected individual, and typically requires medical intervention (46)
Minor congenital malformation	An anomaly or abnormality of body structure that is present at birth, is of prenatal origin (i.e., birth defect), poses no significant health problem in the neonatal period, and tends to have limited social or cosmetic consequences for the affected individual (46)
Congenital/other (structural) abnormality, NOS	Reported congenital anomaly without diagnostic information or other structural anomalies not well described
Abnormality, other (non-structural)	Non-structural abnormalities not related to delivery, other non-structural anomalies not well described, or anomalies reported as normal variant
SGA at delivery	An infant born with a birth weight, length, or head circumference less than the 10th centile on population-level infant birth weight charts
Postnatal growth deficiency	Weight in <10th percentile for sex and chronological age using standard growth charts (47)
Infant developmental delay	Failure to achieve the developmental milestones for chronological age (yes/no). If yes, type of assessment method (CDC, other), type of delay including social/emotional, language/communication, cognitive (learning, thinking, problem-solving) and movement/physical development, diagnosis with free-text comments, date of diagnosis
Neonatal mortality	Death of a live-born infant within 28 days of life
Infant mortality	Death of a live-born infant within 1 year of life
Lost to FU	No further information is received regarding pregnancy outcome event after pursuing appropriate number of FUs for a case

Abbreviations: CDC = Centers for Disease Control and Prevention; FU = follow-up; NOS = not otherwise specified; SGA = small for gestational age

9.3.4.1 Adjudication of outcomes

As part of PRIM enhancements, for each ICSR with reported potential congenital anomaly, i.e., each individual case reporting pregnancy outcome as live birth with a congenital malformation, or other outcome (spontaneous abortion, stillbirth, induced abortion) for which there is evidence of a birth defect, the patient data will be forwarded to independent (external) adjudicators. These cases will be identified from the global safety database as cases with an

AE with seriousness classification "congenital anomaly" and with fetal outcome coded as "congenital anomaly major," "congenital anomaly minor," or "congenital anomaly NOS (structural)." A panel of two independent experts in clinical genetics and neonatology will review all MCMs reported through PV (among eplontersen-exposed pregnancies) and classify them using the European Surveillance of Congenital Anomalies definitions and Metropolitan Atlanta Congenital Defects Program (MACDP) classifications, depending on the region from which the ICSR originated. Additionally, the birth defect evaluators will provide their opinions regarding the timing of the development of observed defects. If there is a discrepancy, a third expert will independently review and code the case, serving as tie breaker. These reviews will occur soon after the MCM is reported to AZ's PV system. Additional reviews will occur if new information is received for the case, as well as the possible temporal association between exposure and the development of observed defects. The sponsor will not be involved in any activities related to case review or adjudication as part of the PRIM approach.

9.3.5 Other variables

Other variables not listed in Sections 9.3.2 and 9.3.3 that are collected and may be used for summarizing patient characteristics or for stratification of description statistics include:

- **PV report characteristics**
  - Date of PV report
  - Type of reporter (whether information is provided by patient, HCP [including role title and specialty], or other)
  - Reporter's name and contact information (telephone number, email address, and address)

- **Maternal demographic characteristics**
  - Date of birth (used to derive age at diagnosis and at conception)
  - Country of residence
  - Race/ethnicity

- **Maternal pre-pregnancy anthropometrics**
  - Body mass index (height and weight)

- **Maternal obstetric history**
  - Number of previous pregnancies, including multiple gestations
  - Outcomes of previous pregnancies (e.g., SAB, stillbirth, induced abortions, live births)
  - Complications of previous pregnancies (e.g., pregnancy-induced hypertension, gestational diabetes, preterm labor, placental disorders, ectopic or molar pregnancies)
  - Characteristics of previous live births (preterm, SGA)
  - Number of previous fetuses/infants with congenital malformations (major and minor)

- **Family history of congenital malformations**
  - Maternal and paternal family history of congenital malformation (major and minor), including specific malformation and relation of family member to mother or father

- **Pregnancy information**
  - Pregnancy status (currently pregnant, recently pregnant)
  - DOC
  - First day of LMP
  - Number of fetuses
  - Maternal age at conception (derived)
  - Consanguinity between parents
  - EDD and method of determination (LMP, ultrasound, ART)
  - Prenatal tests (any prenatal tests including type of test, date of test, and results/findings)
  - Relevant maternal medical conditions, including, but not limited to:
    - Thyroid abnormalities
    - Infectious diseases and infections requiring hospitalizations
    - Asthma
    - Diabetes
    - Hypertension
    - Seizure disorder
    - Autoimmune diseases
    - Heart disease
    - Kidney disease
    - Neurologic disease (e.g., multiple sclerosis)
    - Anemia
    - Depression and other psychiatric disorders
    - Uterine or cervical abnormalities, including congenital uterine abnormalities
    - Cancer
    - hATTR comorbidities and complications:
      - History of transplant (heart, liver, other)
      - Hearing loss
      - Irritable bowel syndrome
      - Cardiac arrhythmias
      - Atrial fibrillation and flutter
      - Cardiovascular disease
    - Other

- **Maternal exposures during pregnancy**
  - Exposure to eplontersen, including indication/reason for use, dose, frequency, and dates/duration of exposure
  - Exposure to other drugs or biological products (including prescription and nonprescription drugs, dietary supplements, vaccines, plasmapheresis, intravenous immune globulin, known teratogens, and investigational

medications), including indication/reason for use, dose, route, frequency, and dates/duration of exposure, if available
    - Vitamin A supplementation including date of initiation, frequency, duration, and dosage of vitamin supplement use
    - Exposure to tobacco, alcohol, marijuana, or other recreational or illicit drugs including timing of exposure if available

- **Index pregnancy outcome characteristics**
    - Date of delivery
    - Gestational age at pregnancy outcome
    - Fetal/infant sex
    - Fetal/infant weight, length, and head circumference
    - Route of delivery (vaginal delivery, elective cesarean, emergency cesarean)
    - For a noninduced fetal loss (SAB, stillbirth), factors that may have had an impact on the fetal loss and attribution
    - For induced abortion, reason (e.g., finding on prenatal test, risk to mother's health, undesired pregnancy)
    - 5-min Apgar score
    - Maternal weight just at (just before) pregnancy outcome

- **Infant outcome information**
    - Infant weight, length, and head circumference at birth (if not provided at pregnancy outcome) and at 6 and 12 months of age
    - Infant illnesses/medical conditions, include cardiovascular conditions (name of condition, date of onset, end date/ongoing)
    - Infant medicinal exposures (indication, dose, start/end date or ongoing)
    - Infant hospitalization (reason for hospitalization, dates of hospitalization or ongoing)
    - Infant death: cause of death, date of death, age at death (derived)
    - Breastmilk feeding information, including breastmilk feeding start/stop dates and maternal medicinal and recreational exposures during breastmilk feeding

9.4 Data sources

This DPSS will utilize secondary data from cases of pregnancy and lactation exposures reported to the AZ PV-Argus as notifiable events under special circumstances relating to pregnancy or lactation exposures, or ADRs reported in pregnancy/lactation in exposed patients, as well as pregnancy- or lactation-associated AEs reported from clinical trials, spontaneous post-marketing reports, post-marketing observational studies, and patient-oriented programs, published literature, and personal communication by HCPs. To encourage spontaneous reporting, an awareness program will be conducted among HCPs and their patients with hATTR-PN and any future approved indications for treatment with eplontersen, with activities including signposting worldwide to the AZ PV system on various websites, as well as via patient advocacy groups and HCP networks in countries with known clusters of hATTR-PN patients.

9.5 Study size

This study is descriptive in nature, and formal sample size calculations were not performed. Precision estimates were calculated based on assumption of five to ten exposures captured during the 10 years of the PRIM program and are displayed below in Table 6. The PRIM program will aim to capture a minimum of five to ten exposures during the study period.

Table 6 Precision calculations for selected outcomes

Outcomes	Reference proportion in general population	Precision with 5 exposures	Precision with 10 exposures
Composite outcome of all MCMs (48)	0.03	(0.00, 0.52)	(0.00, 0.31)
Pregnancy-induced hypertension (49)	0.0647	(0.00, 0.52)	(0.00, 0.45)
Composite outcome of preeclampsia/eclampsia (50)	0.038	(0.00, 0.52)	(0.00, 0.31)
SAB (51)	0.118	(0.01, 0.72)	(0.00, 0.45)
Induced abortion (52)	0.184	(0.01, 0.72)	(0.03, 0.56)
Emergency cesarean (53)	0.067	(0.00, 0.52)	(0.00, 0.45)
Preterm birth (45)	0.0842	(0.00, 0.52)	(0.00, 0.45)
SGA	0.1	(0.00, 0.52)	(0.00, 0.45)
Postnatal growth deficiency	0.1	(0.00, 0.52)	(0.00, 0.45)
Ectopic pregnancy (54)	0.01792	(0.00, 0.52)	(0.00, 0.31)
Stillbirth (55)	0.0057	(0.00, 0.52)	(0.00, 0.31)
Neonatal mortality (56)	0.004	(0.00, 0.52)	(0.00, 0.31)
Infant mortality (56)	0.006	(0.00, 0.52)	(0.00, 0.31)

Abbreviations: MCM = major congenital malformation; SAB = spontaneous abortion; SGA = small for gestational age

9.5.1 Assessment of feasibility

To assess the feasibility of this study, data-based assumptions regarding the prevalence of hATTR-PN, pregnancy, and eplontersen uptake were made to estimate the number of individuals who will potentially be exposed to eplontersen during pregnancy. The mid-range estimate for the number of cases that may exist globally is approximately 10,000 (7). We estimate that no more than 50% of these cases will be female, and with an average age at diagnosis (and therefore treatment) of 64.2 years (standard deviation of 13.6 years), the majority of the hATTR-PN population will be above reproductive age (15–50 years) (12). However, we can estimate that perhaps 10% may be in the reproductive range. Applying the fertility rate for the 40–44-year category (0.0126) yields an estimated six to seven pregnancies per year globally (57). If two of these pregnancies were exposed to eplontersen each year, roughly 20 exposed pregnancies may occur during the study monitoring period. If one-quarter of these were spontaneously reported through PV, the study would be expected to capture five cases over 10 years. Given the rarity of the disease and the estimated number of potentially

exposed cases during the study period, the PRIM approach to the DPSS is thought to be the optimal method for maximizing the capture of exposed cases globally.

9.6 Data management

Data entry will follow applicable AZ processes for ICSRs. Drug exposure and concomitant medications will be coded using the World Health Organization drug dictionary; and outcomes and other variables will be coded using MedDRA terminology and free-text fields, if needed. De-identified data (i.e., removal of reporter name and contact information) collected for each case that meets the inclusion/exclusion criteria will then be extracted from the AZ PV-Argus into a separate database for independent analysis purposes. Follow-up targeted safety questionnaires will be sent to the reporter at set timepoints, depending on when, during the pregnancy/lactation exposure window to eplontersen, the ICSR was initially submitted to AZ PV (for retrospective ICSRs, reported after pregnancy or lactation outcomes, follow-up questionnaire may also be sent if relevant depending on how long after end of exposure these are reported).

Data collection for pregnancy cases will be performed at specific timepoints anchored at the first notification of exposure during pregnancy (with exposures windows classified as preconception, first trimester, second trimester, third trimester, follow-up to first notification to obtain necessary baseline data (baseline characteristics, demographics, etc.), EOP, live births only: EOP date + 180 days (6 months), live births only: EOP date + 365 days (12 months). For pregnancies with a PV initial report before 20 gestational weeks, there will be a data collection point at 24 gestational weeks (±4 weeks). This follow-up timepoint is selected to accurately capture exposure to eplontersen during the first trimester in relation to the primary outcomes of the study. Additionally, 24 gestational weeks corresponds to when pregnancy is considered viable, allowing for more accurate data collection related to spontaneous abortion or medically indicated pregnancy terminations.

Data collection for lactation-only exposed cases will be performed at specific timepoints anchored at first notification of exposure during lactation (date EOP – EOP+365 days); follow-up to first notification to obtain necessary baseline data (baseline characteristics, demographics, etc.); EOP date + 180 days (6 months postpartum); EOP date + 365 days (12 months postpartum). If eplontersen exposure and breastfeeding is ongoing at 8 months post-pregnancy or later, follow-up will be extended an additional 15 weeks to EOP + 470 days. Infant ICSRs up to 12 months of age which are linked to pregnancy/lactation reports in eplontersen-exposed individuals will also be included. Specific details regarding the type of information collected, the time of collection, and the number of attempt cycles are outlined below in Table 7 and Table 8.

Table 7 Pregnancy exposure PV data collection

Follow-up	Information collected	Date of collection	Attempts cycle (in case of no response)[a]
FU1	Reporter type and their contact information, date of report, baseline maternal characteristics and demographics	As soon as possible after the notification report, or at initial report if possible	At least 4 attempts, at a minimum of 1 week and maximum of 1 month apart, unless EOP is reached (in such case merge FU 1 and FU2)
FU2	Reporter type and their contact information, date of report, maternal conditions, relevant fetal information or pregnancy outcome information as applicable	At 24 gestational* weeks for initial report before 20 gestational weeks	At least 4 attempts, at a minimum of 1 week and maximum of 1 month apart
FU3	Reporter type and their contact information, date of report, delivery-related information and neonate details including congenital malformation	EOP	At least 4 attempts, at a minimum of 1 week and maximum of 1 month apart
FU4	Reporter type and their contact information, date of report, information related to infant health status and development including congenital malformation	EOP + 180 days	At least 4 attempts, at a minimum of 1 week and maximum of 1 month apart
FU5	Reporter type and their contact information, date of report, information related to infant health and development including congenital malformations	EOP + 365 days	At least 4 attempts, at a minimum of 1 week and maximum of 1 month apart

Abbreviations: FU = follow-up; EOP = end of pregnancy; PV = pharmacovigilance

[a] Additional FU attempts before a patient is considered "lost to FU." PS Country Teams will routinely make at least four FU attempts at each FU time point before a patient is considered "lost to FU." Such attempts should, when possible, be made simultaneously with the initial reporter and one or more HCPs (when such information is provided), and by all available means of contact (phone, email, letter, fax, etc.) and date of every follow-up contact will be reported.

*There is a ±4 week window for data collection at the 24 weeks FU to ensure maximum data capture.

For lactation, all follow-ups will be collected per the schedule in Table 8.

Table 8 Lactation exposure PV data collection

Follow-up	Information collected	Date of collection	Attempts cycle (in case of no response)[a]
FU1	Reporter type and their contact information, date of report, baseline maternal characteristics and demographics and information related to delivery and neonate details (including congenital malformation) and breastmilk feeding characteristics	At EOP/date of initiation or first notification of exposed lactation, or as soon as possible after the first notification report	At least 4 attempts, at a minimum of 1 week and maximum of 1 month apart
FU2	Reporter type and their contact information, date of report, information related to infant health status and development	EOP + 180 days	At least 4 attempts, at a minimum of 1 week and maximum of 1 month apart
FU3	Reporter type and their contact information, date of report, information related to infant health status and development	EOP + 365 days	At least 4 attempts, at a minimum of 1 week and maximum of 1 month apart
FU4 [b]	Reporter type and their contact information, date of report, information related to infant health and development including congenital malformations	EOP + 470 days	At least 4 attempts, at a minimum of 1 week and maximum of 1 month apart

Abbreviations: FU = follow-up; EOP = end of pregnancy; PV = pharmacovigilance
[a] Additional FU attempts before a patient is considered "lost to FU." PS Country Teams will routinely make at least four FU attempts at each FU time point before a patient is considered "lost to FU." Such attempts should, when possible, be made simultaneously with the initial reporter and one or more HCPs (when such information is provided), and by all available means of contact (phone, email, letter, fax, etc.), and date of every follow-up contact will be reported. [b] FU4 will only occur for cases of eplontersen exposure and breastfeeding that is ongoing at 8 months or later post-pregnancy.

Additional follow-up may be requested in case of congenital anomaly and/or concurrent AEs. Additional follow-up will be done according to applicable standard operating procedures for PV.

9.7 Data analysis

Considering the small number of patients anticipated to be included in this study, it is possible that only case narratives will be developed. However, if at least ten exposed pregnancies are reported, the data will be summarized quantitatively, using relevant measures. Demographic, medical and obstetric history, disease characteristics, eplontersen utilization pattern (during pregnancy and lactation), medicinal and recreational exposures (during pregnancy and

lactation), eplontersen usage characteristics (number of doses, cumulative dose, duration of treatment), pregnancy characteristics, and breastmilk feeding characteristics will be summarized with descriptive statistics for all reported cases (see Section 9.3 for a detailed list of variables to be examined and reported). Continuous variables will be summarized using the number of non-missing values, mean, standard deviation, quartiles, and range. Categorical variables will be reported as numbers and proportions among non-missing. When presented, the 95% confidence intervals (CIs) for proportion of the outcome of interest will be constructed using the exact (Clopper-Pearson) method.

Cases with exposure to eplontersen during pregnancy alone or during pregnancy and lactation will have data collected and reported on all specified maternal, pregnancy, and infant outcomes as listed in Section 9.3.4. For cases with exposure to eplontersen during lactation only, pregnancy and delivery characteristics will be collected, but only maternal and infant events following initiation of breastmilk feeding will be considered outcomes for lactation exposure (e.g., postnatal growth deficiency, infant developmental delay, neonatal death, infant death). Cases exposed during pregnancy will be categorized by earliest trimester of exposure and all cases will be categorized by overall exposure window (pregnancy, lactation, both). This information will be available in listings and, if adequate numbers of cases are identified, will also be summarized in tables.

The frequency, percentage, and, if estimable, 95% CI of the composite of MCMs (as coded by the independent adjudication committee), the composite of minor congenital malformations (as coded by the independent adjudication committee), as well as the other specified outcomes including pregnancy complications (molar or ectopic pregnancy, gestational diabetes, hypertensive disorders of pregnancy, premature rupture of membranes, placental disorders, incompetent cervix, emergency cesarean, maternal hospitalization, maternal death), fetal/neonatal outcomes (SAB, stillbirth, induced abortion), live birth, preterm birth, SGA, neonatal death), and infant outcomes (postnatal growth deficiency, infant developmental delay, infant death) will be reported if appropriate. In addition, MCMs will also be summarized by System Organ Class based on latest available MedDRA classification.

Calculation of percentages for postnatal growth deficiency and infant developmental delay will exclude multiple gestations, as well as singleton infants born preterm or SGA or with MCMs, as these factors are often associated with altered development. Sample size permitting, analyses may be stratified to consider factors such as the timing and extent of exposure, maternal age group at conception, timing of initial PV report (retrospective vs prospective), type of exposure (pregnancy, lactation, both), and reporter type (HCP vs non-HCP). Regardless of sample size, these characteristics will be reported in narratives or listings, as appropriate. All analyses will be conducted using SAS version 9.4 (or higher).

9.8 Quality control

TSQs have been carefully designed to ensure data quality and integrity. AZ will follow its standard operating procedures (SOP) as they relate to training of personnel, data handling, and processing, and comply with appropriate laws. The standard operational procedures for pharmacovigilance will be followed to perform quality control of the data entered to the AZ PV-Argus global safety database. This will include the following steps into Argus: local or global intake of the care report, global case triage, data entry, medical review or medical validation, quality review, case lock, and submission. Additional training for case processors specific to PRIM data collection and entry and additional checks will be implemented on the core data elements to ensure data quality and support for programmatic data summarization. Data recording and documentation retention will follow SOPs defined for collection and retention of data in the AZ PV-Argus global safety database. Reporting activities will follow the SOPs related to programming in the global AZ programming system.

9.9 Limitations of the research methods

The DPSS with PRIM approach is subject to several limitations. Although intensive data collection allows for descriptive analyses and report on prevalence of the outcome, comparative analyses will not be possible in this study as only the eplontersen-exposed cases will be reported to AstraZeneca PV. However, some contextualization of results may be possible using outcome proportions reported through external comparator cohorts such as the MACDP.

Positive case bias is inherent in spontaneous adverse event reporting and this bias may be even more pronounced in retrospectively identified pregnancy cases (where the outcome has already occurred before enrolment). Cases that are initially reported to AZ PV after the pregnancy outcome has occurred (retrospective cases) will be reported separately from those reported before the pregnancy outcome occurs (prospective cases).

As all reported cases of exposed pregnancies and lactation are collected, irrespective of the outcome, the study population may include pregnancies/lactating patients that have no adverse outcomes. However, as this approach is reliant on spontaneous reporting, estimates may be biased if spontaneous reports are more likely to be in individuals experiencing complicated pregnancies or AEs. The study will aim to include all notifiable pregnancies and lactation exposures regardless of disease severity; demographic, medical, and obstetrical characteristics will be described, and over-representation of patients at risk of complicated pregnancies will be discussed in the study reports.

Finally, loss to follow-up is another potential limitation of this DPSS study. Participation in this study is voluntary and reporters can choose to discontinue their participation at any time which could influence the examination of the study objectives. Given that the completion of multiple questionaries is required, such discontinuation may result in a high proportion of

incomplete/missing information which may not be missing at random. Every effort will be made to prevent/minimize such loss to follow-up, such as creating awareness, explaining the importance of the study, and sending reminder messages to complete questionnaires. Descriptive characteristics of individuals lost to follow-up will be reported.

9.10 Other aspects

Not applicable

10. PROTECTION OF HUMAN SUBJECTS

This DPSS will make use of secondary data, consisting of PV reports of eplontersen-exposed pregnant and lactating individuals, that are collected as per good PV practice guidelines and local data privacy laws and de-identified to remove all personal data.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

All data collected via the EPPRO TSQs on reports of exposure to eplontersen during pregnancy or via breastmilk will constitute special situations reports and be entered into the AZ PV-Argus safety database. If AEs or ADRs are recorded in the targeted safety questionnaire, active follow-up will be implemented immediately as described in Section 9.1.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

This DPSS will produce annual interim reports and a final comprehensive study report in 2036, after the conclusion of the DPSS (i.e., after 10 years). These reports will be submitted to the appropriate regulatory authorities. Reports will include a presentation of the DPSS design, methodology, and results to date. The final comprehensive study report will additionally include an interpretative discussion of the biostatistical analysis results.

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Appendix A List of stand-alone documents

None

Appendix B ENCePP checklist for Study protocols

Study title: The Eplontersen Pregnancy and Lactation Outcomes Study (EPPRO): A Descriptive Safety Study of Pregnant and Lactating Individuals and Their Offspring Exposed to Eplontersen

EU PAS Register® number: Not yet registered
Study reference number (if applicable): D8451R00002

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[2]	☒	☐	☐	6
1.1.2 End of data collection[3]	☒	☐	☐	6
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7.4
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	

[2] 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.

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

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
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? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.3.3, 9.3.4
3.4 Does the protocol specify measure(s) of association? (e.g. 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? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.1, 9.2.1
4.2.2 Age and sex	☒	☐	☐	9.2.2
4.2.3 Country of origin	☐	☐	☒	
4.2.4 Disease/indication	☒	☐	☐	9.3.3
4.2.5 Duration of follow-up	☒	☐	☐	9.2.1
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.3, 9.2.4, 9.4

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? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1, 9.3.2
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.3.2
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3.2
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.3.2
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?	☒	☐	☐	9.3.4
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.4
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. 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? (e.g. confounding by indication)	☐	☐	☒	9.9
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. 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? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3.2, 9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.4, 9.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.5, 9.4
9.3 Is a coding system described for:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.6
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.6
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.6
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7
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?	☒	☐	☐	9.7
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? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☐	☒	
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.3.4.1

Comments:

Secondary use of PV data.

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?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. 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? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5.1

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?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9.6, 10

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?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Approved by main author of the protocol: [redacted]

Appendix C Additional information

None