ELAFIBRANOR PREGNANCY SURVEILLANCE PROGRAM: A POST MARKETING, LONG TERM, MULTI-CENTER, NONINTERVENTIONAL AND DESCRIPTIVE STUDY TO CHARACTERIZE PREGNANCY AND MATERNAL COMPLICATIONS AND DESCRIBE EFFECTS ON THE DEVELOPING FETUS, NEONATE AND INFANT AMONG INDIVIDUALS EXPOSED TO ELAFIBRANOR DURING PREGNANCY

STUDY PROTOCOL
STUDY NUMBER: CLIN-60190-471
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Final Version 4.0 (including Amendment #3): 19 May 2026
Final Version 3.0 (including Amendment #2): 23 February 2026
Final Version 2.0 (including Amendment #1): 28 April 2025
Initial Version 1.0: 13 December 2024

Sponsor
Ipsen Biopharmaceuticals
One Main Street
Cambridge, MA, USA

PROTOCOL SIGNATURES

Investigator Signature:

I have read and agree to the Elafibranor Pregnancy Surveillance Program: A Post Marketing, Long Term, Noninterventional and Descriptive Study to Characterize Pregnancy and Maternal Complications and Describe Effects on the Developing Fetus, Neonate and Infant Among Individuals Exposed to Elafibranor During Pregnancy. I am aware of my responsibilities as an investigator under the guidelines of Good Pharmacoepidemiology Practices, Good Pharmacovigilance Practices, any regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME:
TITLE: INVESTIGATOR SIGNATURE: _____

DATE:

Full study site contact details, including telephone numbers, will be documented in the Study Master File.

On behalf of the Sponsor:

NAME: PPD
TITLE: SIGNATURE: _____

DATE:

OFFICE: Ipsen Ltd, UK
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SUMMARY OF CHANGES

The current version of the protocol was released on 19 May 2026 and includes Amendment #3.

	DOCUMENT HISTORY		
Document	Version	Date	Status
Amendment #3	4.0	19 May 2026	Effective
Amendment #2	3.0	23 February 2026	Superseded
Amendment #1	2.0	28 April 2025	Superseded
Initial Protocol	1.0	13 December 2024	Superseded

Amendment 3 (19 May 2026)

This amendment is considered to be substantial based on the criteria set forth in the regulation (EU) No 536/2014.

Overall Rationale for Amendment

The protocol is updated to change the Sponsor name and address.

Summary of changes table from previous version of the protocol

Any new or amended text in the protocol is indicated in bold (IS column). Deletions are marked in strikeout text (WAS column). Minor formatting and editing are not included.

Section	WAS (Version 3.0, 23 February 2026)	IS (Version 4.0, 19 May 2026)	Rationale
Title page	**Sponsor:** **~~Ipsen Pharma SAS~~** **~~70 rue Balard~~** **~~75015Paris~~**	**Sponsor:** **Ipsen Biopharmaceuticals** **One Main Street** **Cambridge, MA, USA**	Change of sponsor.

Other documents impacted:

Informed consent form	Yes ☒	No ☐
Case report form (CRF)	Yes ☐	No ☒
Statistical analysis plan (SAP)	Yes ☐	No ☒

SYNOPSIS

Study Title:	Elafibranor Pregnancy Surveillance Program: A Post Marketing, Long Term, Multi-Center**,** Noninterventional, and Descriptive Study to Characterize Pregnancy and Maternal Complications and to Describe Effects on the Developing Fetus, Neonate and Infant Among Individuals Exposed to Elafibranor During Pregnancy
Short Title	Elafibranor Pregnancy Surveillance Program: A Study to Evaluate the Safety of Elafibranor During Pregnancy
Study Objectives:	Primary objective(s) To describe the occurrence of congenital malformations and developmental delays in the offspring of participants exposed to elafibranor during pregnancy. Secondary objective(s) • To describe the occurrence of minor and major congenital malformations in the offspring of participants exposed to elafibranor during pregnancy. • To describe pregnancy complications in participants exposed to elafibranor during pregnancy. • To describe developmental outcomes in infants and children (up to 2 years of age) born to participants exposed to elafibranor during pregnancy. • To describe maternal complications and outcomes in participants exposed to elafibranor during pregnancy. • To describe the participant's safety and tolerability of elafibranor treatment in pregnancy.
Rationale	The elafibranor pregnancy surveillance program is a comprehensive observational study designed to address critical knowledge gaps regarding the safety of elafibranor exposure in pregnancy. Its primary focus is potential congenital malformations, while also examining a wide range of secondary outcomes including pregnancy complications, fetal development markers, fetal losses and infant health indicators. The program utilizes a multi-faceted approach, gathering data from healthcare providers (HCPs), participants, existing literature, pharmacovigilance (PV) reports (including spontaneous reports, published clinical trial reports and literature reports) to build an understanding of elafibranor's effects in pregnant women, the outcome of their pregnancies and the early development of their offspring.
Brief Summary	The study will include participants who were exposed to at least one dose of elafibranor at any time during pregnancy, or since 3 weeks prior to the conception (based on estimated last menstrual period [LMP]). Information will be collected from participants, their healthcare providers, published studies, and safety databases. Reports of pregnancy linked to elafibranor from clinical trials, spontaneous

	reports, or literature will also be included, with steps taken to avoid duplicates. The study begins once the first virtual site has been initiated and ends after the last mother and child's data are collected. It is planned to run for about 10 years, with infant follow-up lasting up to 2 years, for a maximum total duration of 12 years and 9 months. The program is strictly observational. All medical care, visit schedules, and treatment decisions remain with healthcare providers. Only routine medical record data will be collected, and no extra tests or procedures are required. Participation is voluntary, and written informed consent will be obtained before enrollment.
Study Timelines	The study will be considered to have started when the first virtual site has been initiated. The study will be considered to have ended after the last mother and child's data have been collected. The study is structured with a primary study duration of 10-years, complemented by an additional follow-up period of up to 2-years of infant development. This design allows for a maximum total study duration of 12 years and 9 months from the initial start date, ensuring comprehensive data collection and follow-up. The flexible timeline accommodates participants enrolled at various points throughout the study. For instance, the study has a 10-year recruitment period, with participant follow-up extending up to 2 years and 9 months beyond this period. Individual participant involvement spans from enrollment during pregnancy through their offspring's 2-year follow-up. The final enrolled pregnancy could occur at the end of year 10, with its associated follow-up concluding by the end of year 12.
Study Design:	Participation in the program is entirely voluntary, with enrolled individuals retaining the right to withdraw their consent at any time. The study gathers data from multiple sources, including the enrolled pregnant participant, their HCPs and relevant published clinical reports and literature sources. These HCPs include, but are not limited to, general physicians, midwives, obstetricians, pediatricians, endocrinologists, psychologists, and psychiatrists who are involved in the care of the participant and their offspring during pregnancy and up to 2 years post-delivery. Importantly, the program maintains a strict observational approach, with all treatment decisions, complementary investigations and visit schedules determined by the participants' HCPs. Data for this study will be collected using specially designed paper case report forms (CRFs). This program captures both prospective and retrospective data from various sources. A retrospectively enrolled participant is defined as an individual who is enrolled or for whom initial contact with the

	surveillance program is made after the pregnancy outcome has occurred. For prospectively enrolled participants (i.e. those enrolled prior to pregnancy outcome), pregnancy outcomes will be assessed throughout pregnancy, with data collection occurring at enrollment, at the end of the second trimester, and at pregnancy outcome. Infant outcome data will be collected at approximately 4, 12 and 24 months of infant age. Pregnant women will have the opportunity to self-enroll in the study. Additionally, HCPs will be able to enroll pregnant women. Furthermore, any reports of pregnancy associated with exposure to elafibranor that are captured in the PV safety database e.g. through spontaneous reporting, reports of pregnancy identified during routine PV literature surveillance or reports of pregnancy from clinical trials, will be de-identified and shared with the pregnancy registry. Processes will be in place to identify any duplicate reporting from different sources. For enrolled participants, participation is voluntary, and these participants retain the right to withdraw their consent at any time. This noninterventional study focuses solely on collecting data that are routinely documented in participants medical records as part of standard care. All treatment decisions and scheduling of clinic or hospital visits as well as complementary medical investigations remain under the responsibility of the participants' HCPs. No additional laboratory tests or HCP assessments specifically for the program will be required. To ensure a comprehensive understanding of the impact of elafibranor exposure in pregnancy, the program will also incorporate relevant data from published clinical studies and literature regarding maternal, fetal and infant outcomes associated with exposure to at least one dose of elafibranor at any time during pregnancy, or since 3 weeks prior to the conception (based on estimated LMP). This additional data integration does not require formal enrollment or additional data collection from the sources. In order to ensure data integrity and prevent double counting, the program will implement a rigorous system of unique case identification, data source tracking, and systematic deduplication processes.
Study Population:	The elafibranor pregnancy surveillance program will aim to collect data on individuals who are exposed to at least one dose of elafibranor at any time during pregnancy, or since 3 weeks prior to the conception (based on estimated LMP). While specific enrollment targets are not set due to the anticipated rarity of cases, the program will strive to gather data on as many pregnancies as possible to ensure an assessment of potential risks.
Study Treatment:	This is a noninterventional study.

	The medicinal product elafibranor is prescribed in the usual manner in accordance with the terms of the marketing authorization of the participants' country. The assignment of the participant to a particular therapeutic strategy is not decided in advance by the trial protocol but falls within current practice, and the prescription of the medicine is clearly separated from the decision to include the participant in the study. No additional diagnostic or monitoring procedures are applied to the participants and only epidemiological methods are used for the analysis of collected data.
Study Evaluations:	**Data Sources** Data for this study will be obtained via the following sources: • Participant medical file: the HCP or authorized medical staff will record data from participant's medical files into the CRF at each study center. • Data will be collected from participants and caregivers through CRFs • Relevant data from the PV safety database, including spontaneous and solicited reports from postmarketing sources as well as pregnancy-related information from published clinical studies and literature, including but not limited to journal articles, case reports and systematic reviews. Information will be collected from different sources (e.g., patient, HCP, paediatrician), including comprehensive contact information of participants (e.g., email address and telephone number) with dates of initial and follow-up communication. **Data Collection** Relevant data collected as part of routine medical care will be captured in a CRF. This data will be transmitted to the sponsor for analysis following a validated data transfer process. Data transmitted will be pseudonymized and will be identified by a participant number. The study will utilize forms to collect data throughout its duration. These include the registration form, pregnancy information form, pregnancy outcome form, infant outcomes form, and targeted follow-up form. For each of these forms, the protocol will provide specific details regarding the timing of completion, the potential reporters or sources of the data, and the types of data to be collected. **Primary Safety Endpoint** Prevalence of congenital malformations in elafibranor-exposed pregnancies. **Secondary Safety Endpoints** • Prevalence of minor and major congenital malformations in enrolled study population

	• Prevalence of molar/ectopic pregnancy • Prevalence of fetal loss, including spontaneous abortions (SAB), stillbirths, and terminations (medically indicated or elective or medically indicated abortion) • Prevalence of live births • Prevalence of premature delivery • Prevalence of infants born small for gestational age (SGA) • Prevalence of neonatal/infant death • Prevalence of postnatal growth deficiency at 4 months, 12 months and 24 months • Prevalence of infant developmental delay at 4 months, 12 months and 24 months • Prevalence of infant healthcare requirements and interventions not considered standard, including but not limited to: - Infant hospitalization due to serious illness - Emergency department visits - Specialist or other healthcare professional consultations - Developmental assessments and interventions - Therapeutic services - Educational support and adaptations • Incidence and nature of all adverse events (AEs) in pregnant participants • Changes in biochemical markers of cholestasis from last available measurement before pregnancy and through pregnancy and postpartum: - Alkaline phosphatase - Bilirubin - Alanine aminotransferase - Aspartate aminotransferase - Gamma-glutamyl transferase - Albumin - Bile acids - Creatine phosphokinase - Lipid profile (including total cholesterol, low density lipoproteins [LDL-C], high density lipoprotein [HDL-C], and triglycerides) **Exploratory Endpoints** • All AEs including adverse events of special interest (AESIs) and special situation (SS), clinical laboratory tests, physical examination and vital signs from signing of the informed

	consent form (ICF) up to a period of 2 years post-delivery, will be collected.
Statistical Methods:	**Sample size calculation** The surveillance program will attempt to collect data on all individuals exposed to at least one dose of elafibranor at any time during pregnancy, or since 3 weeks prior to the conception (based on estimated LMP). However, pregnancy exposures are expected to be extremely rare. Given the expected rarity of pregnancy exposures to elafibranor, a formal sample size calculation is not applicable for this surveillance program. Instead, the study will adopt an approach, aiming to identify and collect data on all eligible cases. **Methods** As this is a noninterventional study, no formal statistical testing will be performed, and all the analyses will be primarily descriptive in nature. For each continuous variable, the number of observations, median, mean, standard deviation, interquartile range, minimum and maximum will be reported. For each categorical variable, the frequency and percentage in each category will be reported. The frequency and percentage of participants with missing data for each data point will be presented. Analyses will be conducted in accordance with the study objectives, and applicable guidelines. Statistical analyses will be performed using Statistical Analysis System (SAS)® (version 9.4 or higher). **Analysis of Outcome Measures** The prevalence rates of the outcomes of interest will be calculated and reported on the study population set. To put the surveillance program data into context, background rates of congenital malformations from pregnancy and adverse outcomes from the pregnant population-based surveillance systems and the published literature (e.g. Metropolitan Atlanta Congenital Defects Program, National Vital Statistics System) will be referenced in the report. To contextualize the surveillance program data, outcomes will be compared to those of participants with primary biliary cholangitis (PBC) who became pregnant after their PBC diagnosis but were not exposed to elafibranor, using publicly available literature, as well as considering general population data. The most recent datasets available at the time of reporting, including the latest published data on pregnancy outcomes in women with PBC who were exposed to elafibranor, as well as up-to-date general population pregnancy statistics will be included. **Calculation of Outcome Measures:** For the study, the prevalence of each outcome will be calculated by dividing the number of cases of the outcome by the appropriate denominator for that particular outcome including major and minor congenital malformation, preterm birth SGA, live birth and infant outcomes, postnatal growth deficiency, infant development and

	deficiency hospitalization and spontaneous abortion and preterm birth. **Interim Analysis** The study will include planned interim clinical reports, with the first to be drafted by the end of September 2030. This report will be submitted to the appropriate regulatory authorities. Interim reports will include all data received to date, and data will be summarized separately for the analysis population (i.e. prospectively enrolled participants with HCP-confirmed data, retrospectively enrolled participants, and participants with only self-reported data, cases identified through pharmacovigilance activities, and relevant cases from the published literature).

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1 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	Wording Definition
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMA	Antimitochondrial antibody
ANA	Antinuclear antibodies
AST	Aspartate aminotransferase
CI	Confidence interval
CPK	Creatine phophokinase
CRF	Case report form
EDD	Estimated date of delivery
EU	European union
FDA	Food and drug administration
GCP	Good clinical practice
GGT	Gamma-glutamyl transferase
GPP	Good pharmacoepidemiology practices
GVP	Good pharmacovigilance practices
HCP	Healthcare providers
HDL-C	High density lipoprotein
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IRB	Institutional review board
LDL-C	Low density lipoproteins
LMP	Last menstrual period
MedDRA	Medical dictionary for regulatory activities
PPAR	Peroxisome proliferator-activated receptor
PBC	Primary biliary cholangitis
PV	Pharmacovigilance
PT	Preferred term
SAB	Spontaneous abortions
SAP	Statistical analysis plan

SAE	Serious adverse event
SGA	Small for gestational age
SAS®	Statistical analysis system
SmPC	Summary of product characteristics
SOC	System organ class
SOP	Standard operating procedure
SP	Service provider
SS	Special situation
TFL	Tables, Figures and Listings
US(A)	United States (of America)
USPI	United States prescribing information
UK	United Kingdom
VLDL-C	Very low density lipoprotein

2 INTRODUCTION

2.1 Disease Review

Primary biliary cholangitis (PBC; formerly known as primary biliary cirrhosis [1]) is an autoimmune cholestatic liver disease [2] in which immune-mediated injury is focused on small bile ducts. If left untreated, PBC can lead to liver fibrosis, cirrhosis, hepatocellular carcinoma, liver failure and death [3].

The prevalence of PBC ranges from 2 to 40 per 100,000 worldwide [4, 5]. The female-to-male ratio is 9:1, with the typical participant being a middle-aged female between the age of 40 and 60 years [5]. Primary biliary cholangitis progresses at varying rates, with participants experiencing liver decompensation over a period of several years to decades [6, 7].

One of the complications associated with PBC is the development of hepatocellular carcinoma with an estimated incidence of 0.36 per 100 person years [6]. Extrahepatic autoimmune disorders are present in 40-70% of participants with PBC including Hashimoto's thyroiditis, Sjögren's syndrome, celiac disease, scleroderma, lupus and rheumatoid arthritis [8].

The antimitochondrial antibody (AMA) is a hallmark feature in 90-95% of diagnosed cases [9, 10]. The primary immunological epitope recognized by AMA in the majority of people with PBC is pyruvate dehydrogenase complex, which is an enzyme complex found in the mitochondria and plays an important role in metabolism [9, 10].

In addition to AMAs, 30-50% of participants possess PBC-specific antinuclear antibodies (ANA) that mediate lymphocyte dysregulation causing damage and destruction to the intrahepatic bile ducts [9, 10]. Antinuclear antibodies are markers of a poor prognosis whereas AMAs are not generally reliable indicators of disease severity or progression [10]. Approximately 50% of AMA-negative participants are positive for PBC-specific ANAs [10]. Participants who do not have detectable antibodies may be diagnosed with the disease when they have laboratory and histological features of PBC [11].

Liver chemistries provide early clues to PBC pathology including a disproportionately elevated alkaline phosphatase (ALP), alanine aminotransferase (ALT) and aspartate aminotransferase (AST), elevated γ-glutamyl transferase (GGT) and (to a lesser extent) elevated bilirubin [7].

Participants with PBC may have a spectrum of symptoms. While approximately 60% of participants with PBC are asymptomatic during routine health screenings [5, 6, 7], most may become symptomatic within two to four years of diagnosis [5, 7].

Fatigue present in up to 80% of participants with PBC, is generally considered to be a multifactorial problem and can be disabling [7]. Chronic fatigue may cause daytime sleepiness and cognitive dysfunction [6, 7].

Pruritus is reported in up to 77% of participants with PBC [12] and tends to follow a circadian pattern with symptoms being more severe in the evening and late at night. Pruritus may be localized or diffuse and is often more severe on the arms, legs, feet and hands [7]. Chronic pruritus leads to sleep disturbances, fatigue and depression [5, 6, 7].

Hypercholesterolemia, found in 75-95% of participants with PBC, is not treated unless the participant has comorbidities increasing cardiovascular risk [6, 7, 13].

2.2 Compound Review

IQIRVO® (elafibranor), a peroxisome proliferator-activated receptor (PPAR) agonist, combines the effects of both PPARα and PPARδ activation to modulate bile acid metabolism, bile production and inflammation.

Activation of both PPARα and PPARδ are associated with anti-inflammatory effects by inhibiting the -NF-κB and AP-1 pathways [14] while PPARδ activation has also been shown to

have anti-inflammatory effects through the BCL6-mediated pathway [15]. In addition, PPARα and PPARδ agonists are known to regulate bile acid homeostasis by affecting hepatic bile acid synthesis and excretion as well as the expression of genes related to bile acid metabolism [16]. Their significant effects on reducing serum levels of the bile acid precursor C4, a downstream metabolite of bile acid synthase CYP7A1, as well as total bile acid levels in participants with PBC have been reported [17,18].

Thus, activation of both PPARα and PPARδ modulates complementary pathways and may confer a therapeutic benefit in participants with PBC. Activation of PPAR α and δ might also be effective in reducing the impact of disease by alleviating pruritus [19, 20].

There is limited data on elafibranor use in pregnant women. Animal studies in rats and rabbits have shown reproductive toxicity at clinically relevant exposures, including fetal loss, malformations, stillbirths, and perinatal deaths.

In the European Union (EU), elafibranor is contraindicated during pregnancy as per the summary of product characteristics (SmPC). In the United States, the Food and Drug Administration (FDA) label indicates that elafibranor is not recommended during pregnancy due to the potential risk of fetal harm based on preclinical data. However, adverse events (AEs) were observed in offspring when elafibranor was administered to female rats during pregnancy at clinically relevant exposures.

Given the lack of human data and the potential risk to breastfed infants, elafibranor should not be used during breastfeeding and for at least 3 weeks following the last dose. While this noninterventional study protocol cannot provide specific treatment recommendations, healthcare providers (HCPs) must be aware of and adhere to the current product labeling.

In case of pregnancy, treatment with elafibranor should be discontinued as per the SmPC. Healthcare providers should carefully consider these factors when advising participants of childbearing potential or those who are breastfeeding. It is crucial that HCPs and are regularly reminded of the current label information regarding pregnancy. As a reminder, elafibranor use in pregnancy is not recommended as per the USPI and the United Kingdom-SPC, and is contraindicated as per the EU-SmPC [21,22].

2.3 Study Rationale

The elafibranor pregnancy surveillance program is a comprehensive observational study designed to address critical knowledge gaps regarding the safety of elafibranor exposure during pregnancy. Its primary focus is on potential congenital malformations, while also examining a wide range of secondary outcomes including pregnancy complications, fetal development markers, fetal losses and infant health indicators.

The program utilizes a multi-faceted approach, gathering data from HCPs, participants, existing literature, pharmacovigilance (PV) databases (including spontaneous reports, published clinical trial reports and literature reports), to build an understanding of elafibranor's effects in pregnant women, the outcome of their pregnancies and the early development of their offspring.

By assessing various aspects such as structural abnormalities, gestational diabetes, preeclampsia, fetal growth parameters, miscarriages, stillbirths, birth weights, and early infant development, the study aims to provide a nuanced view of risks. This comprehensive surveillance not only demonstrates a commitment to participant safety but also sets a precedent for thorough drug safety monitoring in vulnerable populations. The results of this program will inform clinical decisions, guide regulatory policies, and contribute to the broader understanding of medication safety during pregnancy, ultimately aiming to improve health outcomes for both mothers and their children while ensuring the responsible use of elafibranor across all participants. The decision to follow children for 2 years post-birth is based on several clinical

and regulatory considerations. According to the European Medicines Agency (EMA) organ maturation tables, the renal, liver, brain, lung, and gastrointestinal systems are either matured or at the later stages of maturation by the age of 2 years. This timeline aligns with recommendations from the National Childbirth Trust, the British Association of Perinatal Medicine, and the National Institute for Health and Care Excellence, all of which conduct or recommend follow-up and developmental assessments until 2 years of age. This 2-year follow-up period allows for assessment of key developmental milestones due to the suitable level of maturation of all necessary organs. However, it's important to note that some behavioral development delays might not be detected until later in childhood, potentially around 5 years of age or beyond. While the 2-year follow-up provides a reasonable and feasible timeframe for initial assessments, longer-term observational studies may be considered in the future to capture any potential later-emerging developmental effects [23, 24, 25].

3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To describe the occurrence of congenital malformations and developmental delays in the offspring of participants exposed to elafibranor during pregnancy.	Prevalence of congenital malformations and developmental delays in the offspring of participants exposed to elafibranor during pregnancy.
Secondary	
To describe the occurrence of minor and major congenital malformations in the offspring of participants exposed to elafibranor during pregnancy.	Prevalence of minor and major congenital malformations in the offspring of participants exposed to elafibranor during pregnancy.
To describe pregnancy complications in participants exposed to elafibranor during pregnancy.	• Prevalence of molar/ectopic pregnancy. • Prevalence of fetal loss, including SAB, stillbirths, live births, preterm birth, neonatal/infant death and terminations (medically indicated or elective).
To describe developmental outcomes in infants and children (up to 2 years of age) born to participants exposed to elafibranor during pregnancy.	• Prevalence of infants born SGA. • Prevalence of postnatal growth deficiency at 4 months, 12 months and 24 months. • Prevalence of infant developmental deficiency at 4 months, 12 months and 24 months. • Prevalence of infant hospitalization due to serious illness.
To describe maternal complications and outcomes in participants exposed to elafibranor during pregnancy.	• Incidence and nature of all adverse events in pregnant participants. • Changes in biochemical markers of cholestasis from last available measurement before pregnancy and through pregnancy and postpartum: - ALP - Bilirubin - ALT - AST - GGT - Albumin - Bile acids

	- CPK - Lipid profile (including total cholesterol, low density lipoproteins, high density lipoprotein, and triglycerides).
Exploratory	
To describe the participant's safety and tolerability of elafibranor treatment in pregnancy.	All AEs including AESIs and SS, clinical laboratory tests, physical examination and vital signs from signing of the ICF until follow-up period, will be collected.

AE=adverse events; AESI=adverse event of special interest; AST=aspartate aminotransferase; ALP=alkaline phosphatase; ALT=alanine transaminase; CPK=creatine phosphokinase; GGT=gamma-glutamyl transferase; ICF=informed consent form; SAB=spontaneous abortion; SGA=small for gestational age; SS=special situations.

4 STUDY DESIGN

This is an international, multicenter, prospective noninterventional pregnancy surveillance program designed primarily to collect and describe comprehensive safety data from pregnancies and outcomes in participants with PBC having had an exposure to at least one dose of elafibranor at any time during pregnancy, or since 3 weeks prior to the conception (based on estimated LMP).

The present study protocol is not a recommendation to expose pregnancies to elafibranor. As this is a noninterventional study, the decision to prescribe the product must be taken prior to, and independently from the decision to enroll the participant, keeping in mind the local label restrictions regarding pregnancy. This decision should be made in accordance with routine/standard clinical practice at the investigational site. The clinical justification for prescribing any treatment should be recorded at the outset by the prescribing clinician, as should the medical decision to pursue treatment prescription once a pregnancy has been confirmed.

4.1 Overview

The elafibranor pregnancy surveillance program is a worldwide, long term, noninterventional and descriptive study to collect comprehensive data on the effects of elafibranor exposure in pregnancy.

Participation in the program is entirely voluntary, with enrolled individuals retaining the right to withdraw their consent at any time. The study gathers data from multiple sources, including the enrolled pregnant participant, their HCPs and relevant published clinical studies and literature articles. These HCPs include, but are not limited to, general physicians, midwives, obstetricians, pediatricians, endocrinologists, psychologists, and psychiatrists who are involved in the care of the participant and their offspring during pregnancy and up to 2 years post-delivery. Importantly, the program maintains a strict observational approach, with all treatment decisions, complementary investigations and visit schedules determined by the participants' HCPs.

Following the United States FDA and Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approvals of the study protocol, participants will be enrolled, and data will be collected. The study is scheduled to be conducted with a planned end date of 2037. Participant follow-up will begin at the time of pregnancy identification in women exposed to at least one dose of elafibranor at any time during pregnancy, or since 3 weeks prior to the conception (based on estimated LMP). This follow-up will also include women who become pregnant within 3 weeks after discontinuing elafibranor, to account for the drug's half-life and potential residual effects.

Data for this study will be collected using specially designed paper case report forms (CRF).

This program captures both prospective and retrospective data from various sources. A retrospectively enrolled participant is defined as an individual who is enrolled or for whom initial contact with the surveillance program is made after the pregnancy outcome has occurred.

For prospectively enrolled participants (i.e. those enrolled prior to pregnancy outcome), pregnancy outcomes will be assessed throughout pregnancy, with data collection occurring at enrollment, at the end of the second trimester, and at pregnancy outcome. Infant outcome data will be collected at approximately 4, 12 and 24 months of infant age.

Retrospectively enrolled participants are further categorized into two groups: fully retrospective (individuals enrolled after both the pregnancy outcome has occurred and the 2-year infant follow-up period has been completed) and partially retrospective (individuals enrolled after the pregnancy outcome has occurred but before the completion of the 2-year infant follow-up period). For fully retrospective participants, all available pregnancy and infant follow-up data

will be collected at enrollment. For partially retrospective participants, historical data on the pregnancy and delivery will be collected at enrollment, while the remaining infant follow-up data will be collected prospectively until the completion of the 2-year follow-up period.

Pregnant women will have the opportunity to self-enroll in the study. Additionally, HCPs will be able to enroll pregnant women. Furthermore, any reports of pregnancy associated with exposure to elafibranor that are captured in the PV safety database e.g. through spontaneous reporting, reports of pregnancy identified during routine PV literature surveillance or reports of pregnancy from published clinical trials, will be de-identified and shared with the pregnancy registry. Processes will be in place to identify any duplicate reporting from different sources.

For enrolled participants, participation is voluntary, and these participants retain the right to withdraw their consent at any time.

This noninterventional study focuses solely on collecting data that are routinely documented in participants' medical records as part of standard care. All treatment decisions and scheduling of clinic or hospital visits as well as complementary medical investigations remain under the decision of the participants' HCPs. No additional laboratory tests or HCP assessments specifically for the program will be required.

To ensure a comprehensive understanding of the impact of elafibranor exposure in pregnancy, the program will also incorporate relevant data from published clinical studies and literature regarding maternal, fetal and infant outcomes associated with exposure to at least one dose of elafibranor at any time during pregnancy, or since 3 weeks prior to the conception (based on estimated LMP). This additional data integration does not require formal enrollment or additional data collection from the sources.

4.2 Population Characteristics

The elafibranor pregnancy surveillance program will aim to collect data on individuals who are exposed to at least one dose of elafibranor at any time during pregnancy, or since 3 weeks prior to the conception (based on estimated LMP).

While specific enrollment targets are not set due to the anticipated rarity of cases, the program will strive to gather data on as many pregnancies as possible to ensure an assessment of potential risks. This includes exposures across different trimesters and varying durations of elafibranor use. To be enrolled in the program, participants must meet all inclusion criteria (detailed in Section 5.1) and not fall under any exclusion criteria (outlined in Section 5.2).

4.3 Study Data Collection

Participants will be treated in accordance with usual medical practice during their participation in this study. No additional assessments or tests will be required by this protocol. This study is noninterventional, thus if some assessments are not routinely performed by the HCP, he/she will not complete the corresponding sections in the CRF.

Data collection for the elafibranor pregnancy surveillance program is designed to be comprehensive and flexible, accommodating both prospective and retrospective cases. For prospectively enrolled participants, data is collected at three key timepoints: enrollment, end of the second trimester and pregnancy outcome. Data will be collected at regular intervals throughout gestation and in the early postnatal period. This will include any occurrences of congenital malformations, premature delivery, early infant loss, spontaneous abortions (SABs), or stillbirths. In the event of any adverse outcomes, including but not limited to early infant loss, detailed information will be collected as soon as possible after the event.

Retrospectively enrolled participants provide all available pregnancy data at the time of enrollment. In both cases, infant outcome data are gathered at approximately 4, 12 and 24 months of age. The program utilizes specially designed CRF to ensure consistent data capture across all participants, regardless of their enrollment method. These methods include self-enrollment by pregnant women, enrollment by HCPs, and reports received by Ipsen PV department. The study adheres to observational principles, collecting only data routinely documented in medical records as part of standard care, without requiring additional tests or assessments. To ensure a comprehensive understanding of the impact of elafibranor exposure in pregnancy, the program will also incorporate relevant data from published clinical studies and literature. A rigorous system of unique case identification, data source tracking, and deduplication processes is implemented to maintain data integrity and prevent double counting.

Relevant data collected as part of routine medical care will be captured in a CRF. This data will be transmitted to the sponsor for analysis following a validated data transfer process. Data transmitted will be pseudonymized and will be identified by a participant number.

4.3.1 Maternal Demographic Characteristics

- Month and year of birth
- Country of residence
- Ethnicity and race in accordance with local regulations and ethical guidelines
- Weight, height
- Risk factors for adverse pregnancy outcomes including environmental or occupational exposures e.g. hypertension, diabetes, seizure disorder, thyroid disorder, asthma, allergic disease, heart disease, depression or other psychiatric disorders, sexual transmitted disorders, hepatitis, acquired immunodeficiency syndrome.
- Medication history, including:
  - Prescription medications
  - Over-the-counter medications
  - Herbal supplements and vitamins
- Occupation, education level
- Substance use:
  - Recreational drug use
  - Alcohol intake (frequency and amount)
  - Tobacco use (including smoking, vaping, and other forms)
  - Pre-pregnancy anthropometrics

4.3.2 Maternal Obstetrical History

Obstetric history will be collected for each participant. This will include the gestational weight, total number of previous pregnancies, pregnancy-related complications (e.g., eclampsia, pre-eclampsia) if any. The outcomes of these prior pregnancies will be documented, categorizing them as spontaneous abortions (SAB), stillbirths, elective or therapeutic abortions or live births. For previous live births, specific characteristics such as premature delivery and small for gestational age (SGA) status will be noted. Additionally, the study will record the number of previous fetuses or infants with congenital malformations, distinguishing between major and minor anomalies, and with neurodevelopmental disorders or psychiatric diseases, and will identify any contributing factors (Table 2).

4.3.3 Family History of Congenital Malformations

- Maternal and paternal family history of congenital malformations (major and minor), including specific malformation, of neurodevelopmental disorders or psychiatric diseases, and relation of family member to mother or father.

4.3.4 Primary Biliary Cholangitis Disease Information

- Data on PBC will be collected, including date of diagnosis, biochemical markers (ALP, ALT, AST, bilirubin, serum bile acids), liver status (fibrosis/cirrhosis staging, transplant history), and participant-reported status of pruritus. These measures will be documented at the last available measurement before pregnancy and throughout the 2-year follow-up period, as available in real-world practice settings transplant.
- The study will document all maternal exposures during pregnancy, who are exposed to at least one dose of elafibranor at any time during pregnancy, or since 3 weeks prior to the conception (based on estimated LMP) with a primary focus on elafibranor use but also including other treatment medications, and non-medicinal substances to comprehensively assess potential influences on pregnancy outcomes. Suspected period will include pregnancy exposure within five times their elimination half-life.

4.3.5 Baseline Pregnancy Information

- The study will record the first day of the LMP and the method of conception for each participant to accurately determine gestational age and assess any potential impact of assisted reproductive technologies on pregnancy outcomes.

4.3.6 Ongoing Pregnancy Information

- Number of fetuses e.g., singleton, multiple (twin, triplets etc.)
- Estimated date of delivery (EDD) and method of determination (i.e. LMP or ultrasound); if ultrasound-determined, timing of ultrasound (before 140/7, before 220/7, or at or after 220/7 gestational weeks). Information on regular prenatal check-up data, maternal health assessments, fetal growth and development markers, pregnancy-related complications (e.g., eclampsia, pre-eclampsia), and importantly, ultrasound measurements of fetal pregnancies.
- Prenatal tests performed, including name of test (e.g. ultrasound, amniocentesis, maternal serum alpha-fetoprotein, chorionic villus sampling), type of test (diagnostic or screening), date of test, and results/findings (e.g. major and minor congenital malformations).
- Medical history of known concurrent risk factors to pregnancy outcomes e.g. diabetes, obesity, alcohol use, prescription medications, substance abuse, cardiovascular disease, hypertension, hyperlipidemia, obstetric complication (e.g. eclampsia, pre-eclampsia premature delivery, and prior intrahepatic cholestasis of pregnancy).

4.3.7 Pregnancy Outcome Information

Pregnancy outcome will be calculated as per classification (mutually exclusive categories) as presented in Table 2.

- Pregnancy type e.g., singleton, multiple (twin, triplets etc.).
- Timing and gestational information: date of pregnancy outcome, gestational weight, gestational age at pregnancy outcome.
- Infant Characteristics (for live births): fetal/infant sex, fetal/infant weight, length, and head circumference at pregnancy outcome.

- Delivery information: route of delivery (i.e. spontaneous vaginal delivery, assisted vaginal delivery or caesarean delivery).
- Major and minor congenital malformations: major or minor and assessment of potential contributing factors
- Additional Information for Specific Outcomes:
  - for a noninduced fetal loss (SAB, stillbirth), factors that may have had an impact on the fetal loss and attribution (e.g. incompetent cervix, previous fetal loss) and
  - for elective or therapeutic abortion, reason (e.g. finding on prenatal test, risk to mother's health, undesired pregnancy).

4.3.8 Infant Data

- Comprehensive infant outcome data will be collected, including demographics, physical examinations, vital signs, laboratory investigations performed and categorized outcomes such as gestational age live birth, preterm birth, stillbirth, termination, spontaneous abortion, as well as detailed descriptions of any congenital malformations (major and minor).
- Data will also be gathered for developmental assessment, neonatal and infant illnesses, hospitalizations, and drug therapies.
- To complement these postnatal data, the study will also incorporate results from anatomical scans performed during pregnancy, and in participants who are exposed to at least one dose of elafibranor at any time during pregnancy, or since 3 weeks prior to the conception (based on estimated LMP). These prenatal imaging studies will provide valuable insights into fetal development, allowing for early detection of potential abnormalities and a more complete picture of fetal health throughout gestation.
- Data will also be gathered on various feeding methods, including direct breastfeeding, feeding with pumped breast milk (bottle feeding), and combination feeding where infants receive both direct breastfeeding and pumped milk.

4.3.9 Other Safety Data

4.3.9.1 Physical Examination

Information on complete physical examination data including a general/overall assessment of skin, ears, nose, throat, neck and thyroid, lung, cardiovascular system, lymph nodes, abdomen (liver and spleen), musculoskeletal system and neurological system will be collected for both mother and infant, at each visit, if available.

Any clinically significant abnormality observed during physical examination will be collected in the AE Form in the paper CRF.

4.3.9.2 Vital Signs

Vital signs (systolic and diastolic blood pressures and heart rate) and weight of the mother and infant will be collected.

Any clinically significant abnormality observed for vital signs will be reported in the AE Form in the CRF.

4.3.9.3 Clinical Safety Laboratory Assessments

The study will collect the following additional clinical laboratory tests data, of the mother and infant, if available.

- Hematology: red blood cell count, hemoglobin, hematocrit, differential white blood cell (WBC) count and platelet count.

- Coagulation test: international normalized ratio, prothrombin time and partial thromboplastin time.
- Serum lipids: triglycerides, total cholesterol, low density lipoprotein (LDL-C), high density lipoprotein (HDL-C), and very low density lipoprotein (VLDL-C).

Any clinically significant abnormal laboratory parameters will be reported in the AE Form in the CRF.

4.4 Study Data Collection Flow

As this is a noninterventional study, treatment with elafibranor, the nature and timing of study visits, and data collection at each visit will be conducted as per routine/clinical practice by local HCP.

Participants can enroll prospectively or retrospectively through self-enrollment, healthcare practitioner referral, or HCP referral, or via de-identified data from PV reports sourced from published clinical trials, observational studies, and spontaneous reports, with the option for interested individuals identified through PV to be referred for self-enrollment, thereby providing informed consent and medical releases to the Vendor Research Coordinating Center.

For prospective cases, data collection occurs at enrollment, end of the second trimester, and pregnancy outcome, while retrospective cases provide all available data at enrollment. Follow-up begins at pregnancy identification for women who are exposed to at least one dose of elafibranor at any time during pregnancy, or since 3 weeks prior to the conception (based on estimated LMP). For participants enrolled retrospectively (i.e. after the pregnancy outcome has occurred), the data collection process is tailored to capture existing information alongside ongoing infant development. At the time of enrollment, all available pregnancy data will be collected. In cases of live births, infant outcome data are collected at 4, 12 and 24 months, with follow-up extending up to 2 years postpartum. The study utilizes standardized paper case report forms, focuses on routinely documented medical data, and incorporates additional relevant information from published clinical studies and literature.

A summary of the data collection process, including the forms that will be used to collect the data, the timing of the completion of each form, the potential reporters or sources of the data, and the types of data that will be collected is presented in Table 1.

Table 1 Summary of Data Collection Process

Data Collection Form	Data Sources/Reporters	Timing of Completion, if Prospectively Enrolled	Data Collected
Registration Form	Identifiable: participant and HCP Nonidentifiable: HCP who enrolled participant, Ipsen PV report	Enrollment	Registration information, including eligibility criteria Maternal demographic characteristics Maternal pre-pregnancy anthropometrics Maternal obstetrical history Family history of congenital malformations Disease information Baseline pregnancy information
Pregnancy Information Form	Identifiable: HCP Nonidentifiable: HCP who enrolled participant, Ipsen PV report	Enrolment, end of 2nd trimester [a] and EDD/pregnancy outcome [a]	Ongoing pregnancy information Maternal exposures during pregnancy
Pregnancy Outcome Form	Identifiable: HCP Nonidentifiable: HCP who enrolled participant, Ipsen PV report	EDD/pregnancy outcome	Pregnancy outcome information
Infant Outcomes Form	Identifiable: HCP Nonidentifiable: HCP who enrolled participant, Ipsen PV report	4, 12 and 24 months after delivery	Breastfeeding information Infant outcome information
Targeted Follow-up Form	Identifiable: HCP Nonidentifiable: HCP who enrolled participant, Ipsen PV report	Any time after pregnancy outcome	Targeted follow-up information

EDD=estimated date of delivery; HCP=healthcare provider; PV=pharmacovigilance.

a Obtain updated information since the previous contact.

Note: HCPs include, but are not limited to, general physicians, midwives, obstetricians, pediatricians, endocrinologists, psychologists, and psychiatrists who are involved in the care of the participant and their offspring during pregnancy and up to 2 years post-delivery.

4.5 Study Data Collection Timing and Methods

For participants enrolled before pregnancy outcome, the study captures data at three crucial junctures: initial registration, mid-pregnancy, and birth or other pregnancy resolution. Those joining the study post pregnancy will be requested to provide a comprehensive retrospective account upon entry. For all participants, infant development is monitored through participant follow-up conducted up to 2 years (Table 1).

4.6 Data Sources

Data for this study will be obtained via the following sources:

- Participant medical file: the HCP or authorized medical staff will record data from participant's medical files into the CRF at each study center.
- Data will be collected from participants and caregivers through CRFs.
- Relevant data from any reports of pregnancy associated with exposure to elafibranor that are captured in the PV safety database e.g. through spontaneous reporting, reports of pregnancy identified during routine PV literature surveillance or reports of pregnancy from clinical trials, will be de-identified and shared with the pregnancy registry. Processes will be in place to identify any duplicate reporting from different sources. Data collection for these cases will occur as part of the routine PV follow-up process and will use forms which are similar to the study data collection forms.

Information will be collected from different sources (e.g., patient, HCP, paediatrician), including comprehensive contact information of participants (e.g., email address and telephone number) with dates of initial and follow-up communication.

4.7 Study Duration/Observation Period

The study will be considered to have started when the first virtual site has been initiated.

The study will be considered to have ended after the last participant and offspring data have been collected.

The study is structured with a primary study duration of 10-years, complemented by an additional follow-up period of up to 2-years of infant development. This design allows for a maximum total study duration of 12 years and 9-months from the initial start date, ensuring comprehensive data collection and follow-up. The flexible timeline accommodates participants enrolled at various points throughout the study. For instance, the study has a 10-year recruitment period, with participant follow-up extending up to 2 years and 9-months beyond this period. Individual participant involvement spans from enrollment during pregnancy through their offspring's 2-year follow-up, not exceeding approximately 3-years per participant. The final enrolled pregnancy could occur at the end of year 10, with its associated follow-up concluding by the end of year 12 and 9-months.

End of the Surveillance Program

The total study duration is set at 12-years and 9 months, comprising a 10-year enrollment period followed by up to 2 years 9 months for pregnancy outcomes and infant follow-up for the enrolled participants.

The total study period may extend to a maximum of 12 years and 9-months from the start date, depending on when participants are enrolled. In accordance with industry guidance on post-approval pregnancy safety studies [26], the surveillance program may be discontinued in any of the following circumstances:

- availability of sufficient information to meet the surveillance program objectives;
- other methods of gathering appropriate information become achievable or are deemed preferable.

Prior to the end of this surveillance program, regulatory authorities will be consulted, as appropriate.

Discussions with Health Authorities will be initiated at the end of the second or third year post-study initiation. These discussions will assess the study's progress, the relevance of the data being collected, and the likelihood of obtaining meaningful information within the planned time-frame.

Based on these assessments, decisions regarding potential early termination or modifications to the study design may be considered. Prior to any early termination, regulatory authorities will

be consulted, as appropriate, to ensure alignment with regulatory expectations and to discuss the implications of the collected data.

4.8 Participant Information

Prior to enrollment of a participant in this study, the designated HCP, will explain the nature and purpose of this data collection to each participant. As all data collection will be conducted in accordance with routine/standard clinical practice, participation in the study does not convey any additional risks or burdens for the participant. The use of elafibranor in pregnancy is subject to different regulatory guidances across various markets. In EU regions, it may be contraindicated, while pregnancy is not contraindicated as per the FDA label but does include special warnings or precautions for use in pregnant women. Healthcare providers should refer to their local product labeling for specific guidance.

In regions where elafibranor is not contraindicated during pregnancy, it is generally not recommended for use during pregnancy due to potential risks to the fetus. Healthcare providers should carefully advise participants of child-bearing potential or those who become pregnant while taking elafibranor of the potential risk to the fetus. It is crucial that HCPs and participants are aware of and adhere to the most current local regulatory guidance and product labeling regarding the use of elafibranor during pregnancy.

Written informed consent must be obtained prior to participant enrollment and prior to any data being entered in the study database. Sufficient time should be allowed to discuss any questions raised by the participant. The participants should be allowed as much time as they need to consider their decision.

The sponsor will provide the informed consent form (ICF), in a language readily understandable by the participant. The ICF should be personally signed and dated by the participant/caregiver and, by the person who conducted the informed consent discussion and should be retained by the HCP. The HCP will provide all enrolled participants/caregivers with a copy of their signed informed consent.

The ICF and any participant recruitment materials will follow international ethical guidelines, applicable local regulatory and legal requirements, including applicable privacy laws across all centers. The consent form will be revised during the study if any new safety information becomes available.

5 STUDY POPULATION

5.1 Inclusion Criteria

Each individual must meet all of the following criteria to be eligible to participate in this study:

(1) Maternal exposure to at least one dose of elafibranor, either:
   (a) Within three weeks prior to conception (based on the estimated date of LMP)
   OR
   (b) At any time during pregnancy (from the estimated date of conception through pregnancy outcome).

(2) Participants who were previously enrolled in this program during a past pregnancy and who meet inclusion criteria #1 for the subsequent pregnancy are eligible to enroll again.

(3) Informed consent or IRB/IEC-approved waiver of informed consent (not applicable if reported by Ipsen PV according to usual PV practices).

5.2 Exclusion Criteria

Individuals who meet the following criterion will not be eligible to participate in this study:

(1) Participant with mental instability or incompetence, such that the validity of informed consent or ability to be compliant with the study is uncertain.

5.3 Participant Withdrawal Criteria

As this is a noninterventional study, participants will be managed according to each clinical center's medical routine/standard practice, therefore no specific withdrawal criteria are specified.

Participants are free to withdraw consent at any time. The HCP may withdraw a participant from the study at any time for safety reasons or at his/her discretion. Data will be collected up to the time of withdrawal, with no additional information collected thereafter.

For participants who withdraw from the study, the End of Study visit will be the visit where withdrawal details are recorded (Early Withdrawal visit). Any AEs collected/reported will, however, be followed-up until resolved or stabilized or until the participant is lost to follow-up.

In case the participant is withdrawn from the study, the primary reason for withdrawal should be recorded in the CRF.

6 STUDY ENDPOINT AND EVALUATIONS

6.1 Safety Endpoints and Evaluations

6.1.1 Primary Safety Endpoint

Prevalence of congenital malformations.

6.1.2 Secondary Safety Endpoints

- Prevalence of minor and major congenital malformations
- Prevalence of molar/ectopic pregnancy
- Prevalence of fetal loss, including SAB, stillbirths, and terminations (medically indicated or elective or medically indicated abortion)
- Prevalence of live births
- Prevalence of premature delivery
- Prevalence of infants born SGA
- Prevalence of neonatal/infant death
- Prevalence of postnatal growth deficiency at 4 months, 12 months and 24 months
- Prevalence of infant developmental delay at 4 months, 12 months and 24 months
- Prevalence of infant healthcare requirements and interventions not considered standard, including but not limited to:
  - Infant hospitalization due to serious illness
  - Emergency department visits
  - Specialist or other healthcare professional consultations
  - Developmental assessments and interventions
  - Therapeutic services
  - Educational support and adaptations
- Incidence and nature of all adverse events (AEs) in pregnant participants
- Changes in biochemical markers of cholestasis from last available measurement before pregnancy and through pregnancy and postpartum:
  - ALP
  - Bilirubin
  - ALT
  - AST
  - GGT
  - Albumin
  - Bile acids
  - Creatine phosphokinase (CPK)
  - Lipid profile (including total cholesterol, LDL-C, HDL-C, VLDL-C and triglycerides)

6.1.3 Outcome Definitions and Ascertainment

The evaluation of outcomes for this study, encompassing both primary and secondary endpoints (Section 6.1.1 and Section 6.1.2), will be conducted through a comprehensive analysis of data collected via the standardized forms outlined in Table 1. These forms serve as crucial instruments for capturing a wide range of clinical, physiological, and developmental parameters

throughout the pregnancy and postpartum periods. By leveraging the information gathered from these carefully designed forms, researchers can systematically assess the impact of the treatment or condition on maternal health, pregnancy progression, fetal development, and infant outcomes. For outcomes not simply reported by the HCP, additional information on outcome ascertainment is provided.

The definitions of the outcomes are presented in Table 2.

Table 2 Outcome Definitions and Ascertainment

Outcome	Definition [a]	Ascertainment
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 [27]	The surveillance program defines and codes MCMs with criteria specified by CDC MACDP [28]. If participants who reside in Europe are enrolled, MCMs will also be defined and coded using the criteria specified by EUROCAT [29; Appendix 1]. Exclusion criteria for analyses: To avoid misattribution of the malformation to the medication, MCMs not known to be associated with medication exposure, such as chromosomal abnormalities, genetic syndromes, prematurity-related conditions in infants born at <36 gestational weeks (e.g. patent ductus arteriosus, patent foramen ovule, inguinal hernias, or undescended testes), and positional effects (e.g. hip dislocation due to breech position or abnormal skull shape due to crowding by multiple fetuses), will not be considered MCMs in the statistical analyses [30]. Adjudication process: An independent expert in clinical genetics and neonatology will review all malformations reported from any source and classify them using the CDC's MACDP system (and EUROCAT, if applicable). Additionally, the birth defect evaluator will provide the organ system involved, etiology of the defect (e.g. chromosomal abnormality, prematurity), and approximate timing of the development of observed defects. If additional information is needed to aid in classification, the birth defect evaluator will request additional information using the targeted follow-up questionnaire. This evaluation will occur soon after the malformation is reported. Additional reviews will occur if new information is received for the case.
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 [27]	The surveillance program defines and codes minor congenital malformations with criteria specified as defined by CDC [28]. The same process for adjudicating MCMs will be used to adjudicate minor congenital malformations.
Molar or ectopic or pregnancy	Molar pregnancy is defined as an abnormal pregnancy that happens when a sperm fertilizes an egg that does not contain any genetic material. Ectopic pregnancy is defined as a pregnancy that occurs outside of the uterine cavity, usually in one of the fallopian tubes [32].	-
Fetal loss	A fetal loss that occurs for any reason at any time during pregnancy.	
Spontaneous abortion (SAB)	An involuntary fetal loss or the expulsion of the products of conception occurring at <20 gestational weeks.	-

Outcome	Definition [a]	Ascertainment
Stillbirth	As defined by the ACOG, an involuntary fetal loss occurring at ≥20 gestational weeks or, if gestational age is unknown, a fetus weighing ≥350 g [33].	-
Elective or therapeutic abortion	A voluntary fetal loss or interruption of pregnancy that occurs for any reason, including but not limited to for the preservation of maternal health or due to fetal abnormalities.	-
Fetal loss, unspecified	A fetal loss that is not reported as SAB, stillbirth, or elective therapeutic abortion.	-
Live birth	The birth of a living fetus at ≥ 20 gestational weeks or, if gestational age is unknown, weighing ≥ 350 g.	-
Premature delivery	A live birth occurring at <37 gestational weeks.	-
Preeclampsia	Pre-eclampsia is a disorder of pregnancy that is associated with new-onset hypertension (defined as a systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg), most often after 20 weeks' gestation and frequently near term.	
Small for gestational age (SGA)	Birth weight <10th percentile for sex and gestational age using standard growth charts for full and preterm live-born infants [34].	For the determination of SGA, the surveillance program will utilize the sex-specific international growth reference standards from the INTERGROWTH-21st for those born between 240/7 and 426/7 gestational weeks [35; 36]. The INTERGROWTH-21st standards are the latest available global reference standards, representing contemporary information from an international, multiethnic, diverse population, and have been specifically developed for modern research.
Neonatal death	Death of a live-born infant within the first 28 days of life	-
Infant death	Death of a live-born infant within first year of life	-
Postnatal growth deficiency	Weight, length, or head circumference in <10th percentile for sex and age using standard growth charts	Postnatal growth deficiency will be evaluated at 4, 12 and 24 months of infant age; deficiencies in weight, length, and head circumference will be evaluated separately. For the determination of postnatal growth deficiency, the surveillance program will utilize the sex-specific international growth reference standards from the WHO for children ages 0 to 59 months. The WHO growth standards are recommended for use in the US for infants and children 0 to 2 years of age [37].

Outcome	Definition [a]	Ascertainment
Infant developmental delay	Failure to achieve the developmental milestones for chronological age, as defined by the CDC [38].	Infant developmental delay will be evaluated at 4, 12 and 24 months of infant age for each CDC-defined category (social/emotional, language/communication, cognitive, and movement/physical development), separately. HCPs will indicate on the data collection forms whether infants are meeting CDC-defined milestones (yes/no) for each category and age. Infants who are failing to achieve at least one milestone in any category will be considered developmentally delayed in that category.
Infant hospitalization due to serious illness	Infant hospital visits due to a serious (i.e. results in significant disability, incapacity, or death; is life-threatening; requires in-patient or prolonged hospitalization; or is considered medically important) illness	-

ACOG=American College of Obstetricians and Gynecologists; CDC=Centers for Disease Control and Prevention; EUROCAT=European Registration of Congenital Anomalies and Twins; HCP=healthcare provider; INTERGROWTH-21st=International Fetal and Newborn Growth Consortium for the 21st Century; MACDP=Metropolitan Atlanta Congenital Defects Program; MCM=major congenital malformation; SAB=spontaneous abortion; SGA=small for- gestational age; US=United States; WHO=World Health Organization.

a When information on the presence or absence of congenital malformations is available, it must be captured and documented in detail, regardless of the pregnancy outcome or infant status.

6.1.4 Adverse Events and Special Situations

All AEs and adverse event of special interest (AESI), whether they are serious/nonserious, related/unrelated, and all "special situations (SS)" will be assessed according to incidence, intensity, causality, outcome, action taken and seriousness.

The definition of AEs and serious adverse events (SAEs) can be found in Section 9.1.

The HCP and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE, AESI or SAE and remain responsible for following up any AEs or SAEs (Section 9.3).

For the management and reporting of the AEs, AESIs and specials situation, please refer to Section 9.2.1.

6.1.5 Exploratory Endpoints

- Complete physical examination assessment
- Changes in vital signs (systolic and diastolic blood pressures and heart rate) from last available measurement before pregnancy and through pregnancy and postpartum
- Changes in safety lab parameters from last available measurement before pregnancy and through pregnancy and postpartum

7 TREATMENTS OF INTEREST

This is a noninterventional study designed to characterize pregnancy and maternal complications and describe effects on the developing fetus, neonate and infant among individuals who are exposure to at least one dose of elafibranor at any time during pregnancy, or since 3 weeks prior to the conception (based on estimated LMP). The decision to prescribe elafibranor will be made/was made prior to and independently of the decision to enroll the participant in this noninterventional study and should comply with the locally approved label.

8 STATISTICAL CONSIDERATIONS

The information provided in this section may be subject to changes that will be indicated in the final Clinical Study Report of this study. A Statistical Analysis Plan (SAP) may be developed as a separate document and approved prior to database lock, if deemed appropriate.

8.1 Participant Classification and Definitions

Enrolled participant	Participant who signed informed consent
Valid participant	Participant with minimum data required for enrollment
Prospective participant	Participant for whom initial contact with the surveillance program is made before the pregnancy outcome has occurred
Participant lost to follow-up	Participant with no follow-up information obtained: no pregnancy outcome information, no follow-up data after birth for live-born infants

8.2 Definition of Analyses Populations

Enrolled Set:	All participants who signed informed consent. This set will be used to summarize participant disposition.
Safety Set:	All enrolled participants who were exposed to at least 1 dose of elafibranor and fulfill the eligibility criteria as well as their offspring exposed to at least 1 dose during pregnancy. This set will be used to summarize safety.
Study Population Set:	All enrolled participants who were exposed to at least 1 dose of Elafibranor, fulfill the eligibility criteria, are valid, prospective, with health care practitioner (HCP) confirmed data and is not lost to follow-up. All live birth offsprings of these participants, regardless of gestational age at birth, will be included in the follow-up and analysis of infant outcomes.

8.2.1 Populations Analyzed

The outcomes analysis will be based on the study population set. For the analyses of preterm birth, SGA, and postnatal growth deficiency, multiple gestation pregnancies will additionally be excluded from the analysis population.

Retrospectively enrolled participants and participants with only participant-reported data will be included in supplementary analyses.

8.2.2 Participant Allocation and Reasons for Exclusion from the Analyses

The rules for the allocation of participants to each of the analysis populations will be defined and documented during a data review meeting held prior to database lock.

During the data review meeting, based on minor or major protocol deviations recorded, participants may be excluded from the study population set.

8.3 Sample Size Determination

The surveillance program will attempt to collect data on all individuals exposed to elafibranor at any time from the date of LMP through pregnancy outcome. However, pregnancy exposures are expected to be extremely rare.

Given the expected rarity of pregnancy exposures to elafibranor, a formal sample size calculation is not applicable for this surveillance program. Instead, the study will adopt an approach, aiming to identify and collect data on all eligible cases.

8.4 Statistical and Analytical Methods

Statistical analyses will be performed using Statistical Analysis System (SAS)® (version 9.4 or higher).

As this is a noninterventional study, no formal statistical testing will be performed, and all the analyses will be primarily descriptive in nature.

For each continuous variable, the number of observations, median, mean, standard deviation, interquartile range, minimum and maximum will be reported. For each categorical variable, the frequency and percentage in each category will be reported. The frequency and percentage of subjects with missing data for each data point will be presented. Results will be rounded off to one decimal place; therefore, percentages may not always add up to 100.

Analyses will be conducted in accordance with the study objectives, and applicable guidelines.

The definition and coding system for birth defects, minor and major malformations used in this study are detailed in Appendix 1, ensuring standardized classification and reporting of these outcomes.

8.4.1 Demographic and Other Baseline Characteristics

Descriptive summary statistics (n, mean, 95 % confidence interval [CI] of the mean, standard deviation, median, minimum, maximum) or frequency counts of demographic and baseline data will be presented as overall, for the enrolled safety set.

8.4.2 Participant Disposition and Withdrawals

The numbers and percentages of participants in the enrolled population will be tabulated by country and center. The reasons for participant exclusions from each of the populations will also be tabulated. In addition, the number of participants who withdraw along with their primary reasons for withdrawal will be tabulated.

8.4.3 Safety Analysis

Safety analysis will be performed on the safety population.

Analysis of AEs

An overall summary table of all AEs (including fatal events) will be presented with the number and proportion of participants and the number of events. Summary tables of all AEs, AESIs, SAEs and AEs by relationship to study drug and intensity will be provided, classified by primary System Organ Class (SOC) and Preferred Term (PT).

All AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and will be classified by MedDRA PT and SOC.

Listings of all AEs, AESIs, SAEs, AEs leading to study drug withdrawal and deaths will be provided.

Analysis of "Special Situations"

"Special situations" will be listed separately, and summary table will be provided.

Analysis of Cholestasis and Safety Biochemical Markers

This analysis is particularly important given elafibranor's intended use in treating cholestatic liver diseases. The study will evaluate several key aspects:

- Temporal Comparisons: The analysis will compare biochemical marker levels at different time points - before pregnancy, during each trimester of pregnancy, and postpartum. This longitudinal approach will help identify any changes in liver function associated with pregnancy and/or elafibranor use.
- Specific Markers: The study will focus on key indicators of cholestasis and liver function, including serum bile acids, ALP, GGT, ALT, AST total bilirubin, CPK and lipid profile (including total cholesterol, LDL-C, HDL-C, VLDL-C, and triglycerides).

For each parameter, actual values and change from last available measurement before pregnancy will be summarized using descriptive statistics.

8.4.4 Analysis of the Outcome Measures

The prevalence rates of the outcomes of interest will be calculated and reported on the study population set. To put the surveillance program data into context, background rates of congenital malformations from pregnancy and adverse outcomes from the pregnant population-based surveillance systems and the published literature (e.g. Metropolitan Atlanta Congenital Defects Program, National Vital Statistics System) will be referenced in the report. To contextualize the surveillance program data, outcomes will be compared to those participants with PBC participants who became pregnant after their PBC diagnosis but were not exposed to elafibranor using publicly available literature, as well as considering general population data.

The most recent datasets available at the time of reporting, including the latest published data on pregnancy outcomes in women with PBC who were exposed to elafibranor, as well as up-to-date general population pregnancy statistics will be included.

8.4.4.1 Calculation of the Outcome Prevalence

For the study, the prevalence of each outcome will be calculated by dividing the number of cases of the outcome by the appropriate denominator for that particular outcome (Table 3).

Prevalence is preferred over incidence when examining pregnancy outcomes, such as congenital malformations, because incidence cannot be reliably estimated given the complexities in the reproductive process.

- Major and minor congenital malformations: The prevalence will be calculated among participants exposed to elafibranor at any point during pregnancy. This broad approach ensures capturing all potential effects of the drug. Additionally, a more focused analysis will be conducted specifically for first-trimester exposure, for fetal development and teratogenic effects.
- Preterm Birth, SGA, and postnatal growth deficiency: For these outcomes, the prevalence will be calculated only among singleton live births. This exclusion of twins and higher-order multiples is crucial because these pregnancies inherently carry a higher risk for these outcomes.
- Live birth and infant outcomes: These include preterm birth, SGA, neonatal death, infant death, postnatal growth deficiency, infant developmental delay, and infant hospitalization due to serious illness. The prevalence for these outcomes will be calculated among live births and infants without congenital malformations. This approach helps isolate the effects of elafibranor from those caused by congenital abnormalities.
- Postnatal growth deficiency: In this calculation, infants born preterm or SGA will be excluded from the denominator. This exclusion is important because these infants are already at higher risk for growth issues, and their inclusion could mask the true effect of elafibranor on postnatal growth.

- Infant developmental deficiency and hospitalization: Preterm infants will be excluded from the denominator for both these outcomes, as preterm birth itself is associated with developmental delays and increased risk of hospitalization, which could confound the results.
- Spontaneous abortion and preterm birth: The prevalence of these outcomes will be calculated among participants enrolled before specific gestational ages - 20 weeks for SAB and 37 weeks for preterm birth. This approach ensures that the denominator includes only those pregnancies that were at risk for these outcomes. The presence and detailed description of any associated minor and major congenital malformations will be documented and analyzed for these cases, providing crucial information on potential links between elafibranor exposure and fetal development abnormalities.

Table 3 Calculation of Outcome Prevalence

Outcome	Numerator	Denominator
Primary analysis	Live births and stillbirths with confirmed CMs (including CMs not associated with medication exposure) among individuals with pregnancy outcome data and exposure during the 1st trimester	Live births and stillbirths among individuals with pregnancy outcome data and exposure during the 1st trimester
Secondary analysis	Live births and stillbirths with confirmed CMs (excluding CMs not associated with medication exposure) among individuals with pregnancy outcome data and exposure during the 1st trimester	Live births and stillbirths among individuals with pregnancy outcome data and exposure during the 1st trimester
Minor congenital malformations	Live births with minor congenital malformations among individuals with pregnancy outcome data	Live births among individuals with pregnancy outcome data
Major congenital malformations	Live births with major congenital malformations among individuals with pregnancy outcome data	Live births among individuals with pregnancy outcome data
Molar or ectopic pregnancy	Ectopic and molar pregnancies among individuals with pregnancy outcome data	Individuals with pregnancy outcome data
Fetal loss	Fetal losses, including SABs, stillbirths, elective or therapeutic abortions, and losses with unknown type, among individuals with pregnancy outcome data	Individuals with pregnancy outcome data
SAB	SABs among individuals with pregnancy outcome data who are enrolled and exposed prior to 20 gestational weeks	Individuals with pregnancy outcome data who are enrolled and exposed prior to 20 gestational weeks
Stillbirth	Stillbirths among individuals with pregnancy outcome data	Live births and stillbirths among individuals with pregnancy outcome data
Elective or therapeutic abortion	Elective or therapeutic abortions among individuals with pregnancy outcome data	Live births among individuals with pregnancy outcome data
Live birth	Live births among women with pregnancy outcome data	Women with pregnancy outcome data
Premature delivery	Singleton preterm live births without CMs among individuals with pregnancy outcome data who are enrolled and exposed prior to 37 gestational weeks	Singleton live births without CMs among individuals with pregnancy outcome data who are enrolled and exposed prior to 37 gestational weeks
Preeclampsia	Pre-eclampsia is a disorder of pregnancy that is associated with new-onset hypertension (defined as a systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg), most often after 20 weeks' gestation and frequently near term.	

Outcome	Numerator	Denominator
SGA	Singleton live births without CMs who SGA are based on weight among individuals with pregnancy outcome data	Singleton live births without CMs with weight data among individuals with pregnancy outcome data
Neonatal death	Infant deaths that occur at 0-27 days of life among infants without MCMs and with at least 1 follow-up completed	Infants without CMs and with at least 1 follow-up completed
Infant death	Infant deaths that occur within first year of life among infants without CMs and with data up to 24 months of age	Infants without CMs and with data up to 12 months of age
Postnatal growth deficiency (at 4,12 and 24 months)	Singleton infants without CMs who were not born preterm, SGA with postnatal growth deficiency based on weight among infants with weight data at the timepoint	Singleton infants without CMs who were not born preterm, SGA with weight data at the timepoint
Infant developmental deficiency (at 4,12 and 24 months)	Infants without CMs who were not born preterm with developmental deficiency in a particular category among infants with developmental milestone data for the category at the timepoint	Infants without CMs with developmental milestone data for the category at the timepoint
Infant hospitalization due to serious illness	Infants without CMs who were not born preterm, with a qualifying hospitalization from birth to 24 months of age and among infants with hospitalization data up to 24 months of age	Infants without CMs who were not born preterm with hospitalization data up to 24 months of age
CM=congenital malformation; SAB=spontaneous abortion; SGA=small for gestational age.		

8.4.4.2 Subgroup Analyses

To provide a more comprehensive analysis, the program will include a sub-analysis specifically examining events potentially related to elafibranor exposure.

Analyses include:

(1) Prospectively enrolled participants lost to follow-up: Participant who ceased participation in the study prior to the planned end of follow-up of the study.

(2) Retrospectively Enrolled Participants: This group consists of individuals who were enrolled in the study after their pregnancy had already begun or ended. While pregnancy data may be subject to recall bias, it can still provide valuable insights, especially for rare outcomes or long-term effects. For offspring of these participants:

- If enrolled before the child reaches 2 years of age, prospective follow-up will continue until the child's second birthday.
- If enrolled after the child's second birthday, all offspring data will be retrospective.

(3) Participants with Only Self-reported Data: This analysis will include participants whose outcome data was not confirmed by an HCP. While potentially less reliable than HCP-confirmed data, self-reported information can capture a broader range of experiences and may highlight issues that warrant further investigation.

8.5 Interim Analysis

The study will include planned interim clinical reports, with the first to be drafted by the end of September 2030. This report will be submitted to the appropriate regulatory authorities. Interim reports will include all data received to date, and data will be summarized separately for the study population set (i.e. prospectively enrolled participants with HCP-confirmed data), retrospectively enrolled participants, and participants with only self-reported data, cases identified through pharmacovigilance activities, and relevant cases from the published literature).

9 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE DRUG REACTIONS AND SPECIAL SITUATIONS

9.1 Definition

9.1.1 Adverse Event

AE Definition
An Adverse Event is any untoward medical occurrence in a participant/participant, administered a medicinal product and which does not necessarily have a causal relationship with this treatment. NOTE: An AE can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of the medicinal product, whether or not related to the medicinal product.

Events Meeting the AE Definition
Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the HCP (i.e. not related to progression of underlying disease). Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. New condition detected or diagnosed after study treatment administration even though it may have been present before the start of the study. Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. For studies involving marketed products in established indications include: The signs, symptoms, and/or clinical sequelae resulting from lack of effectiveness will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of effectiveness" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT Meeting the AE Definition
Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the HCP to be more severe than expected for the participant's condition. The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. Medical or surgical procedure (e.g. endoscopy, appendectomy): the condition that leads to the procedure is the AE.

Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

9.1.2 Serious Adverse Event

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g. hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires in-patient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in persistent disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Other Important Medical Event Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

9.1.3 "Special Situations"

Special situation is any incidence of drug exposure during breastfeeding, overdose, off-label use, medication errors, occupational exposure, abuse, misuse or lack of therapeutic

effectiveness while using the medicinal product. A "special situation" should be collected by the HCP and reported to Ipsen whether or not these "special situations" are associated with an AE.

9.1.3.1 Overdose, Off-label Use, Misuse, Abuse, Occupational Exposure, and Medication Error

Overdose

Any dose higher than the maximum recommended dose in local label/SmPC, or in the protocol. For products which require gradual titration, any dose (initial or maintenance) which is higher than the recommended regime in the protocol, or labeling text will be assessed as 'overdose'. Overdoses should be reported as AEs in the AE CRF page whether or not they were associated with a clinical event. All overdoses should be reported to Ipsen within 7 calendar days using the Ipsen Adverse Event and Special Situations Reporting Form for Noninterventional Studies (134232-FOR).

Off-label Use

Off-label use relates to situations where the medicinal product is intentionally used for a medical purpose not in accordance with the terms of the marketing authorization Off-label use should be reported as AEs in the AE CRF page whether or not they were associated with a clinical event. All Off-label use should be reported to Ipsen within 7 calendar days using the Ipsen Adverse Event and Special Situations Reporting Form for Noninterventional Studies (134232-FOR).

Misuse

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the marketing authorization.

Misuse should be reported as AEs in the AE CRF page whether or not they were associated with a clinical event. All misuse should be reported to Ipsen within 7 calendar days using the Ipsen Adverse Event and Special Situations Reporting Form for Noninterventional Studies (134232-FOR).

Abuse

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Abuse should be reported as AEs in the AE CRF page whether or not they were associated with a clinical event. All abuse should be reported to Ipsen within 7 calendar days using the Ipsen Adverse Event and Special Situations Reporting Form for Noninterventional Studies (134232-FOR).

Occupational exposure

Occupational exposure refers to the exposure to a medicinal product, as a result of one's professional or nonprofessional occupation. It does not include the exposure to one of the ingredients during the manufacturing process before the release as finished product.

Occupational exposure should be reported as AEs in the AE CRF. All occupational exposure should be reported to Ipsen within 7 calendar days using the Ipsen Adverse Event and Special Situations Reporting Form for Noninterventional Studies (134232-FOR).

Medication error

Medication error is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the participant.

Medication error should be reported as AEs in the AE CRF whether or not they were associated with a clinical event. All medication error should be reported to Ipsen within 7 calendar days using the Ipsen Adverse Event and Special Situations Reporting Form for Noninterventional Studies (134232-FOR).

9.1.4 Adverse Events of Special Interest

Adverse events of special interest are AEs that may or may not be serious but are of special importance to a particular drug or class of drugs. The severity of all AEs and SAEs, including the AESIs, will be documented as described in Section 9.2.

- The AESIs for this study are defined according to categories below follows:

9.1.4.1 Muscle Injury

- Creatine phosphokinase elevations of severe intensity or leading to permanent study drug discontinuation.
- Muscle injury symptoms of severe intensity corresponding to:
  - Muscle pain or myalgia;
  - Muscle spasms or tremor;
  - Muscle weakness.

9.1.4.2 Liver Injury

- Transaminases elevations from baseline of severe intensity or leading to permanent study drug discontinuation.
- Liver injury events of severe intensity corresponding to:
  - Hepatic injury;
  - Hepatic impairment;
  - Hepatic failure.

9.2 Time Period and Frequency for Collecting and Reporting AE, AESI, SS and SAE Information

For the definition of the AEs, AESI and specials situation (SS), please refer to Section 9.1.

9.2.1 Collection of the AEs/SAEs/AESI/SSs in the CRF

The collection and reporting of AEs will follow regulations related to noninterventional studies.

All AEs, whether they are serious/nonserious, related/unrelated, and all special situations should be collected in the CRF during the course of the study. Adverse events will be assessed according to incidence, intensity/grade, causality, outcome, action taken and seriousness.

All AEs which occurred during the study period, will be collected in the CRF.

All AEs reported spontaneously by the participant or observed by the healthcare provider during routine clinical practice will be documented in the CRF. The collection period for AEs begins from the time of informed consent and continues throughout the participant's participation in the study, which may vary depending on individual circumstances and the timing of routine clinical visits.

9.2.2 Reporting of SAEs, Nonserious Adverse Drug Reactions, AESIs and SSs to Sponsor Pharmacovigilance

Health care practitioners must report to Ipsen PV all the following events using the "Adverse Event and Special Situation Reporting Form for noninterventional Studies" (134232-FOR):

- All SAEs – related and not related;
- All AESIs – related and not related
- All related nonserious AE/ADRs (Adverse Drug Reactions (ADRs));
- Any special situation (see definitions in Section 9.1).

Primary Data Collection NIS		
Safety Event	**Collected on the CRF**	**Reported on the « AE NIS Form » to Ipsen Global Pharmacovigilance**
Nonserious adverse event (AE)	All AEs related or not	Only the Related AEs - within 7 calendar days of awareness
Serious adverse event (SAE)	All SAEs related or not	All - within 24 hours of awareness
Adverse event of Special Interest (AESI)	All AESI related or not	All – within 24 hours of awareness
Special Situations (SS)	All SS related or not (regardless of whether associated with an AE)	All (regardless of whether associated with an AE) - within 7 calendar days of awareness

For combined studies with a design based on both secondary use of data and primary data collection, the safety reporting requirements for each phase of the study must follow the AE and SAE reporting requirements as for primary data collection studies.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours (once known), as indicated below. The HCP will submit any updated SAE data to the sponsor within 24 hours of it being available.

All nonserious related AEs and special situations will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 7 calendar days (once known), as indicated below.

SAE Reporting to Ipsen Pharmacovigilance via specific NIS AE Form

To report initial or any follow-up information to Ipsen, a completed ***Adverse Event and Special Situations Reporting Form for Noninterventional Studies*** (134232-FOR) should be sent to the following within 24 hours of awareness of the event for a SAE or AESI and within 7 calendar days for a nonserious related AE and SS:

Email: PPD

NOTE: If SAEs are being reported to a service provider (SP), add phone number if required by the SPs Standard Operating Procedures (SOPs); a SP phone number is not required if SAEs are being reported directly to Ipsen.

SAE Reporting to Ipsen Pharmacovigilance via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the sponsor. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the HCP to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in PPD

All adverse events will be processed by Ipsen according to their relevant SOP. This includes the follow-up of adverse event reports with the HCP, as required.

If an AE occurs with a "non-Ipsen product", the investigator should consider informing the competent authority in the Member State where the event occurred or to the marketing authorization holder of the suspected medicinal product, but not to both (to avoid duplicate reporting).

Mandatory Information for Reporting an Adverse Event

The following information is the minimum that must be provided to Ipsen's pharmacovigilance contact within 24 hours for a SAE and within 7 days for a nonserious related AE of awareness for each adverse event:

- Participant identifier
- Product name
- Adverse Event description including assessment of causal relationship and seriousness
- Health care practitioner name and contact details.

The additional information included in the adverse event report form must be provided to Ipsen as soon as it is available.

The HCP should report a diagnosis or a syndrome rather than individual signs or symptoms. The HCP should also try to separate a primary adverse event considered as the foremost untoward medical occurrence from secondary adverse events which occurred as complications. The HCP should also provide the batch number and expiry date of the concerned product wherever possible.

9.3 Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE/related AE reports are provided below.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the HCP to review all documentation (e.g. hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The HCP will then record all relevant AE/SAE information in the CRF.
- It is not acceptable for the HCP to send photocopies of the participant's medical records to Sponsor in lieu of completion of the AESI/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor.
- The HCP will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The HCP will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The HCP is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The HCP will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The HCP will also consult the Product Information, for marketed products, in his/her assessment.

- For each AE/SAE, the HCP must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the HCP has minimal information to include in the initial report to Sponsor. However, it is very important that the HCP always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor.
- The HCP may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

9.4 Follow-up of AEs and SAEs

After the initial AE/SAE/AESI report, the HCP is required to proactively follow each participant at subsequent visits/contacts. All SAEs, AEs and AESIs (as defined in Section 9.1.2 and Section 9.1.4 when applicable), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.

Follow-up of AEs and SAEs

- The HCP is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the HCP will provide Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The HCP will submit any updated SAE data to Sponsor within 24 hours of receipt of the information.

9.5 Regulatory Reporting Requirements for SAEs/Related AEs

- Prompt notification by the HCP to the sponsor of a SAE/related AE is essential so that legal obligations and ethical responsibilities towards the safety of participants.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of any medicinal product. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- An HCP who receives an HCP safety report describing a SAE or other specific safety information (e.g. summary or listing of SAEs) from the sponsor will review and will notify the IRB/IEC, if appropriate according to local requirements.

9.6 Expectedness of Events

The reference document for assessing expectedness of AEs/event in this study will be the locally approved SmPC or prescribing information (PI).

The expectedness of an AE shall be determined by the sponsor according to the SmPC or PI for an authorized medicinal product that is being used according to the terms and conditions of the marketing authorization. If the product has marketing authorizations in several countries with different SmPCs or PIs, one will be selected by the sponsor as the reference document for assessing expectedness.

10 STUDY MANAGEMENT

10.1 Monitoring Procedures

The HCP is responsible for the integrity of all data collected at the study center.

As this is a noninterventional study, traditional monitoring procedures are not compulsory. However, to maintain data quality and study integrity, all activities will be completed in accordance with Ipsen and the SP's SOPs and as per the monitoring plan. The monitoring of the study should ensure that the rights and wellbeing of the participants are protected, that the data are accurate (complete and verifiable to source data) and that the study is conducted in compliance with the protocol and regulatory requirements. The frequency of the monitoring may be adapted according to participant recruitment rate or any other suitable reason.

The HCP will allow direct access to all relevant files (for all participants) for the purpose of verifying entries made in the CRF and assist with the monitor's activities, if requested. Adequate time and space for monitoring visits should be made available by the HCP.

The HCP must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the participant's file. The HCP must also keep the original ICF signed by the participants as well as by their caregivers (if applicable) and a signed copy is given to them.

The HCP must complete the CRFs in a timely manner and on an ongoing basis to allow regular review by the monitor.

Whenever a participant name is revealed on a document required by the sponsor, the name must be blacked out permanently by the study personnel annotated with the participant number as identification.

10.2 Recording of Study Data

In compliance with Good Pharmacovigilance Practice, the medical records/medical notes, should be clearly marked and permit easy identification of a participant's participation in this study.

Paper CRF will be utilized for collecting participant data.

10.3 Data Verification on Site

Within the framework of a noninterventional study, only the following source data verification will be performed by the sponsor:

Definition for source data and source documents are given below:

Source Data:	All original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source Documents: Original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, participant's diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

The sponsor assigned HCP must verify, by direct reference to the medical records/medical notes, that the data required by the protocol are accurately reported on the CRF.

The medical records/medical notes must, as a minimum, contain the following; a statement that the participant is included in the study (with corresponding study number).

The participant must have consented to their medical records being viewed by sponsor-authorized personnel, and by local, and possibly foreign, CAs. This information is included in the ICF.

10.4 Data Quality

The CRF data will be reviewed for completeness, consistency and protocol compliance.

Data consistency and accuracy will be check at time of data entry. Queries will be raised as needed for clarification/correction.

The reporter should provide handwritten signature to attest to the accuracy and completeness of all the data.

10.5 Data Management

Data management will be conducted by a SP, directed by the sponsor's Global Medical Affairs Biometry department. All data management procedures will be completed in accordance with Ipsen and the contracted SP SOPs.

The sponsor will ensure that an appropriate CRF is developed to capture the data accurately.

Control procedures of the reliability and validity of collected data using the paper CRF will be defined and described in a Data Validation Plan (DVP). These procedures will be defined to ensure the validity of the data considering the study objectives and context. These controls will focus on the completeness and the plausibility of the recorded values (controls of bounds) and the compatibility between the data (consistency check).

Prior to a database lock, a data review meeting will be held to review and document all inconsistencies. All decisions made during this data review, prior to the analysis, will be recorded in a specific report maintained in the study repository.

Once data review meeting minutes are approved, the participants' database will be locked and transmitted to the statistician for analysis.

10.6 Record Archiving and Retention

The HCP (or authorized medical staff) will be responsible for maintaining a centralized and understandable filing system of all the documentation related to the study. These documents should be available at any time and kept in a secure place after the final report or first publication of study results as per local law. These documents may be inspected in an audit by Ipsen representatives and/or the Competent Authorities at any time.

This documentation will include an exact copy of the CRF and the study file with the protocol (and any amendments), any documentation related to the study and any correspondence related

to the study. All the original source documents from which the information is registered in the CRF should be kept up-to-date and available easily.

No document related to the study should be destroyed without prior written authorization between Ipsen and the HCPs. In case the HCPs would like to transmit these files to another person or move them to another place, (s)he shall notify Ipsen specifying the person in charge of and/or the new address.

11 ETHICAL CONSIDERATIONS, REGULATORY FRAMEWORK, AND ADMINISTRATION PROCEDURES

11.1 Ethical and Regulatory Considerations

This study is noninterventional and falls outside the scope of the EU Directive 2001/20/EC [39], the EU Directive 2005/28/EC [40] and International Council for Harmonisation-Good Clinical Practice guidelines.

This study must be conducted in compliance with the recommendations of the Declaration of Helsinki [41] and the International Ethical Guidelines for Epidemiological Studies, Council for International Organizations of Medical Sciences, 2009 [42].

This study complies with the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of individuals with regards to the processing of personal data and on the free movement of such data [43].

This study will also follow the recommendations of the International Epidemiological Association Guidelines for the Proper Conduct in Epidemiologic Research [44] and the International Society for Pharmacoepidemiology (ISPE) Good Pharmacoepidemiological Practices (GPP) Guidelines [45].

Safety data collection and reporting should be consistent with EU Good Pharmacovigilance Practice (GVP) [46,47] unless dictated by relevant local legislation for safety reporting in which case that must be followed instead.

In addition, this study will adhere to all local regulatory requirements applicable to noninterventional studies.

Before initiating the study, the HCP/institution should have written and dated approval/favorable opinion from the Independent Ethics Committee/Independent Review Board as applicable.

As required by applicable local regulations, the sponsor's Regulatory Affairs group will ensure all legal regulatory aspects are covered, and obtain approval of the appropriate regulatory bodies, prior to study initiation in regions where an approval is required.

Insurance may be contracted according to local regulatory requirements.

11.2 Publication Policy

Ipsen is committed to disclosing information about the studies it sponsors. Results will be communicated at scientific meetings and all reasonable efforts must be made to seek publication in a peer-reviewed scientific journal. Specific publication concepts, including data to be covered, target congress/journal and proposed authors, should be discussed with the appropriate Global Publications Manager and incorporated in the relevant publication plan before initiation. A dedicated Publications Committee, involving interested members of the study Steering Committee as well as the Global Publications Manager, may be established to plan specific publications. As a minimum, summary results of this study should be posted on the relevant study registry. When the study has been conducted by a large multicenter group, the principal HCP, the study Steering Committee (if applicable) and Ipsen's responsible physician should discuss and agree the selection of authors for planned publications in advance. They may decide to use a group name and nominate authors on behalf of the study group. All contributing HCPs will be listed in the acknowledgements together with any others who may have contributed but not sufficiently to qualify for authorship.

Selection of authors for scientific publications will follow the International Committee of Medical Journal Editors guidelines [http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html]. In particular, those named

as authors, whether employed by Ipsen or an Ipsen affiliate, or external HCPs, 'should have participated sufficiently in the work to take public responsibility for the content'.

Authorship should be based on:

- Substantial contributions to the conception and design, or acquisition of data, or analysis and interpretation of data; AND
- Drafting the article or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects for the work, thereby ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

All authors of a publication should meet all four criteria. Each author must agree to their inclusion in the list of authors. Use of professional medical writing support may be employed.

Resolution of scientific differences in the presentation or interpretation of study findings will be conducted along principles of honest scientific debate. The sponsor shall be promptly notified of any amendments subsequently requested by referees or journal editors.

All publications arising from this study will be reviewed by relevant functions at Ipsen, coordinated by the Global Publications team as per the applicable SOP. Requests and suggestions for changes will be discussed with all authors (and medical writer, if applicable). Resolution of scientific differences in the presentation or interpretation of study findings will be conducted along principles of honest scientific debate. Review comments must be answered before a final version for submission can be approved by the author team.

11.3 Study Report

A study report will be prepared in compliance with any applicable regulatory requirements, national laws in force. It should be written in English.

11.4 Contractual and Financial Details

The HCP (and/or, as appropriate, the hospital administrative representative) and the sponsor will sign a clinical study agreement prior to the start of the study, outlining overall sponsor and HCP responsibilities in relation to the study. Financial remuneration will cover the cost per included participant, and the specified terms of payment will be described in the contract.

12 PROTOCOL AMENDMENTS

In the event of an amendment to this protocol, the HCP/institution will ensure that a written and dated approval/favorable opinion from the IEC/IRB, as applicable, has been obtained for the amended protocol.

Amendment 1 (28 April 2025)

This amendment is considered to be substantial based on the criteria set forth in the regulation (EU) No 536/2014.

Overall Rationale for Amendment

The protocol was updated so that data collection regarding maternal gestational weight and preeclampsia could be collected as advised by Food and Drug Administration (FDA).

Summary of changes table from previous version of the protocol

Any new or amended text in the protocol is indicated in bold (IS column). Deletions are marked in strikeout text (WAS column). Minor formatting and editing are not included.

Section	WAS (Version 1.0, 13 December 2024)	IS (Version 2.0, 28 April 2025)	Rationale
Cover page	Sponsor Ipsen Pharma SAS ~~65 quai Georges Gorse~~ ~~92100 Boulogne-Billancourt~~ France Tel: +33 1 58 33 50 00	Sponsor Ipsen Pharma SAS **70 rue Balard** **75015 Paris** France Tel: +33 1 58 33 50 00	Ipsen office address is updated to current address.
Synopsis (Study Evaluation)/ Section 4.6	[,..]	[…] **Information will be collected from different sources (e.g., patient, HCP, paediatrician), including comprehensive contact information of participants (e.g., email address and telephone number) with dates of initial and follow-up communication.**	Protocol is updated as advised by FDA.
Synopsis (Study evaluation)/ Section 6.1.2	Secondary Safety Endpoints: […] • Prevalence of live births • Prevalence of ~~preterm birth~~ • Prevalence of infants born small for gestational age (SGA) • Prevalence of neonatal/infant death • Prevalence of postnatal growth deficiency at 4 months, 12 months and 24 months • Prevalence of infant developmental delay at 4 months, 12 months and 24 months • Prevalence of infant healthcare requirements not considered standard, including but not limited to: - Infant hospitalization due to serious illness - Emergency department visits - Specialist or other healthcare professional consultations - Developmental assessments and interventions - Therapeutic services - Educational support and adaptations	Secondary Safety Endpoints: […] • Prevalence of live births • Prevalence of **premature delivery** • Prevalence of infants born small for gestational age (SGA) • Prevalence of neonatal/infant death • Prevalence of postnatal growth deficiency at 4 months, 12 months and 24 months • Prevalence of infant developmental delay at 4 months, 12 months and 24 months • Prevalence of infant healthcare requirements **and interventions** not considered standard, including but not limited to: - Infant hospitalization due to serious illness - Emergency department visits - Specialist or other healthcare professional consultations - Developmental assessments and interventions - Therapeutic services - Educational support and adaptations	The text is updated to keep be consistent within draft

Synopsis (Statistical Methods)	[…] ~~A Statistical Analysis Plan (SAP) describing the planned statistical analysis in detail will be developed as a separate document.~~		
Section 4.3.2	Obstetric history will be collected for each participant. This will include the total number of previous pregnancies, if any. The outcomes of these prior pregnancies will be documented, categorizing them as spontaneous abortions (SAB), stillbirths, elective or therapeutic abortions or live births. For previous live births, specific characteristics such as ~~preterm~~ delivery and small for gestational age (SGA) status will be noted. Additionally, the study will record the number of previous fetuses or infants with congenital malformations, distinguishing between major and minor anomalies, and identifying any contributing factors (Table 2).	Obstetric history will be collected for each participant. This will include the **gestational weight**, total number of previous **pregnancies, pregnancy-related complications (e.g., eclampsia, pre-eclampsia)** if any. The outcomes of these prior pregnancies will be documented, categorizing them as spontaneous abortions (SAB), stillbirths, elective or therapeutic abortions or live births. For previous live births, specific characteristics such as **premature** delivery and small for gestational age (SGA) status will be noted. Additionally, the study will record the number of previous fetuses or infants with congenital malformations, distinguishing between major and minor anomalies**, and with neurodevelopmental disorders or psychiatric diseases**, and **wil**l identify any contributing factors (Table 2).	Protocol is updated as advised by FDA.
Section 4.3.6	• Number of fetuses [...] • Medical history of known concurrent risk factors to pregnancy outcomes e.g. diabetes, obesity, alcohol use, prescription medications, substance abuse, cardiovascular disease, hypertension, hyperlipidemia, eclampsia, pre-eclampsia, and prior intrahepatic cholestasis of pregnancy).	• Number of fetuses **e.g., singleton, multiple (twin, triplets etc.)** [...] • Medical history of known concurrent risk factors to pregnancy outcomes e.g. diabetes, obesity, alcohol use, prescription medications, substance abuse, cardiovascular disease, hypertension, hyperlipidemia, **obstetric complications (eg** eclampsia, pre-eclampsia, **premature delivery** and prior intrahepatic cholestasis of pregnancy).	Protocol is updated as advised by FDA (Food and Drug Administration.

Section 4.3.7	Pregnancy outcome will be calculated as per classification (mutually exclusive categories) as presented in Table 2. • Timing and gestational information: date of pregnancy outcome, gestational age at pregnancy outcome. • Infant characteristics (for live births): fetal/infant sex, fetal/infant weight, length, and head circumference at pregnancy outcome.	Pregnancy outcome will be calculated as per classification (mutually exclusive categories) as presented in Table 2. • **Pregnancy type e.g., singleton, multiple (twin, triplets etc.)** • Timing and gestational information: date of pregnancy outcome, **gestational weight**, gestational age at pregnancy outcome. • Infant characteristics (for live births): fetal/infant sex, fetal/infant weight, length, and head circumference at pregnancy outcome.	Protocol is updated as advised by FDA.
Section 4.3.8	[…]	[…] • Data will also be gathered for developmental assessment, neonatal and infant illnesses, hospitalizations, and drug therapies.	Protocol is updated as advised by FDA.
Section 6.1.3 and Section 8.4.4.1		Tables 2 and 3 updated with definition of Preeclampsia	Protocol is updated as advised by FDA.
Section 8	The information provided in this section may be subject to changes that will be indicated in the final ~~Statistical Analysis Plan (SAP)~~ of this study. ~~The~~ SAP will be developed as a separate document and approved prior to database lock, ~~containing a description of the planned statistical analysis in detail with Tables, Figures and Listings (TFL) templates.~~	The information provided in this section may be subject to changes that will be indicated in the final **Clinical Study Report of this study. A** Statistical Analysis Plan (SAP) may be developed as a separate document and approved prior to database lock, **if deemed appropriate.**	Protocol is updated as advised by FDA.
Section 8.4	~~A SAP describing the planned statistical analysis in detail with TFLs templates will be developed as a separate document.~~ Statistical analyses will be performed using Statistical Analysis System (SAS)® (version 9.4 or higher). As this is a noninterventional study, no formal statistical testing will be performed, and all the analyses will be primarily descriptive in nature	Statistical analyses will be performed using Statistical Analysis System (SAS)® (version 9.4 or higher). As this is a noninterventional study, no formal statistical testing will be performed, and all the analyses will be primarily descriptive in nature	Protocol is updated as advised by FDA.

Amendment 2 (26 February 2026)

This amendment is considered to be substantial based on the criteria set forth in the regulation (EU) No 536/2014.

Overall Rationale for Amendment

The protocol was updated to (1) remove the mention of lactation in the objectives as the collection of data during lactation period was initially not intended to be covered by this protocol, (2) clarify baseline and definition of exposure, (3) correct the type of ultrasound data collected, (4) align section 9.2.2 with general safety reporting rules presented in the protocol and (5) add short title and brief summary information.

Summary change table from previous version of the protocol

Any new or amended text in the protocol is indicated in bold (IS column). Deletions are marked in strikeout text (WAS column). Minor formatting and editing are not included.

Section	WAS (Version 2.0, 28 April 2025)	IS (Version 3.0, 23 February 2026)	Rationale
Synopsis (Short title)		**Elafibranor Pregnancy Surveillance Program: A Study to Evaluate the Safety of Elafibranor During Pregnancy**	Protocol updated with addition of short title.
Synopsis (Study Objectives)	Secondary objective(s) • To describe the occurrence of minor and major congenital malformations in the offspring of participants exposed to elafibranor during pregnancy. • To describe pregnancy complications in participants exposed to elafibranor during pregnancy. • To describe developmental outcomes in infants and children (up to 2 years of age) born to participants exposed to elafibranor during pregnancy ~~and/or lactation~~. • To describe maternal complications and outcomes in participants exposed to elafibranor during pregnancy. • To describe the participant's safety and tolerability of elafibranor treatment in pregnancy.	Secondary objective(s) • To describe the occurrence of minor and major congenital malformations in the offspring of participants exposed to elafibranor during pregnancy. • To describe pregnancy complications in participants exposed to elafibranor during pregnancy. • To describe developmental outcomes in infants and children (up to 2 years of age) born to participants exposed to elafibranor during pregnancy. • To describe maternal complications and outcomes in participants exposed to elafibranor during pregnancy. • To describe the participant's safety and tolerability of elafibranor treatment in pregnancy.	Protocol updated to remove lactation.
Synopsis (Brief summary)		The study will include participants who were exposed to at least one dose of elafibranor at any time during pregnancy, or since 3 weeks prior to the conception (based on estimated last menstrual period [LMP]). Information will be collected from participants, their healthcare providers, published studies, and safety databases. Reports of pregnancy linked to elafibranor from clinical trials, spontaneous reports, or literature will also be included, with steps taken to avoid duplicates. The study begins once the first virtual site has been initiated and ends after the last mother and child's data are collected. It is planned to run for about 10 years, with infant follow-up lasting up to 2 years, for a maximum total duration of 12 years and 9 months. The program is strictly observational. All medical care, visit schedules, and treatment decisions remain with healthcare providers. Only routine medical record data will be collected, and no extra tests or procedures are required. Participation is voluntary, and written informed consent will be obtained before enrollment.	Protocol updated with addition of brief summary.
Synopsis (Study Timelines)	The study will be considered to have started when the first ~~participant has signed the informed consent (if applicable).~~ The study will be considered to have ended after the last ~~participant~~ and ~~offspring~~ data have been collected.	The study will be considered to have started when the first **virtual site has been initiated**. The study will be considered to have ended after the last **mother** and **child's** data have been collected.	Protocol updated to align with operational aspects.

Synopsis (Study design)	Pregnant women will have the opportunity to self-enroll in the study. Additionally, HCPs will be able to enroll pregnant women. Furthermore, any reports of pregnancy associated with exposure to elafibranor that are captured in the PV safety database e.g. through spontaneous reporting, reports of pregnancy identified during routine PV literature surveillance or reports of pregnancy from clinical trials, will be de-identified and shared with the pregnancy registry. Processes will be in place to identify any duplicate reporting from different sources. ~~The same data collection forms will be used for all participants, regardless of how they entered the study~~. For enrolled participants, participation is voluntary, and these participants retain the right to withdraw their consent at any time. […] To ensure a comprehensive understanding of the impact of elafibranor exposure in pregnancy, the program will also incorporate relevant data from published clinical studies and literature regarding maternal, fetal and infant outcomes associated with exposure to at least one dose of elafibranor at any time during pregnancy, or since 3 weeks prior to ~~their LMP, or within 3 weeks of elafibranor discontinuation~~. This additional data integration does not require formal enrollment or additional data collection from the sources.	Pregnant women will have the opportunity to self-enroll in the study. Additionally, HCPs will be able to enroll pregnant women. Furthermore, any reports of pregnancy associated with exposure to elafibranor that are captured in the PV safety database e.g. through spontaneous reporting, reports of pregnancy identified during routine PV literature surveillance or reports of pregnancy from clinical trials, will be de-identified and shared with the pregnancy registry. Processes will be in place to identify any duplicate reporting from different sources. For enrolled participants, participation is voluntary, and these participants retain the right to withdraw their consent at any time. […] To ensure a comprehensive understanding of the impact of elafibranor exposure in pregnancy, the program will also incorporate relevant data from published clinical studies and literature regarding maternal, fetal and infant outcomes associated with exposure to at least one dose of elafibranor at any time during pregnancy, or since 3 weeks prior to **the conception (based on estimated LMP)**. This additional data integration does not require formal enrollment or additional data collection from the sources.	Protocol updated as different forms are used as described in Section 4.4.
Synopsis (Study population)	The elafibranor pregnancy surveillance program will aim to collect data on individuals who are exposed to at least one dose of elafibranor at any time during pregnancy, or since 3 weeks prior to ~~their last menstrual period (LMP), or within 3 weeks of elafibranor discontinuation~~. While specific enrollment targets are not set due to the anticipated rarity of cases, the program will strive to gather data on as many pregnancies as possible to ensure an assessment of potential risks.	The elafibranor pregnancy surveillance program will aim to collect data on individuals who are exposed to at least one dose of elafibranor at any time during pregnancy, or since 3 weeks prior to **the conception (based on estimated LMP**). While specific enrollment targets are not set due to the anticipated rarity of cases, the program will strive to gather data on as many pregnancies as possible to ensure an assessment of potential risks.	Definition of exposure has been corrected throughout the protocol to align with the wording of inclusion criterion #1.

Synopsis (Study evaluations)	**Data Sources** Data for this study will be obtained via the following sources: • Participant medical file: the HCP or authorized medical staff will record data from participant's medical files into the CRF at each study center. • Data will be collected from participants and caregivers through CRFs • Relevant data from the PV safety database, ~~which collates~~ pregnancy-related information from published clinical studies and literature, including but not limited to journal articles, case reports and systematic reviews. […] • Changes in biochemical markers of cholestasis from ~~baseline (before conception or at elafibranor initiation)~~ through pregnancy and postpartum: - Alkaline phosphatase - Bilirubin - Alanine aminotransferase - Aspartate aminotransferase - Gamma-glutamyl transferase - Albumin - Bile acids - Creatine phosphokinase - Lipid profile (including total cholesterol, low density lipoproteins, high density lipoprotein, and triglycerides) **Exploratory Endpoints** All AEs including adverse events of special interest (AESIs) and special situation (SS), clinical laboratory tests, physical examination and vital signs from signing of the informed consent form (ICF) up to a period of ~~3 years after starting elafibranor treatment~~, will be collected.	**Data Sources** Data for this study will be obtained via the following sources: • Participant medical file: the HCP or authorized medical staff will record data from participant's medical files into the CRF at each study center. • Data will be collected from participants and caregivers through CRFs • Relevant data from the PV safety database, **including spontaneous and solicited reports from postmarketing sources as well as** pregnancy-related information from published clinical studies and literature, including but not limited to journal articles, case reports and systematic reviews. […] • Changes in biochemical markers of cholestasis from **last available measurement before pregnancy and** through pregnancy and postpartum: - Alkaline phosphatase - Bilirubin - Alanine aminotransferase - Aspartate aminotransferase - Gamma-glutamyl transferase - Albumin - Bile acids - Creatine phosphokinase - Lipid profile (including total cholesterol, low density lipoproteins, high density lipoprotein, and triglycerides) **Exploratory Endpoints** All AEs including adverse events of special interest (AESIs) and special situation (SS), clinical laboratory tests, physical examination and vital signs from signing of the informed consent form (ICF) up to a period of **2 years post-delivery**, will be collected.	Protocol updated to specify the forms used to collect PV data. The word baseline has been removed and replaced by last available measurement before pregnancy which better translates the actual data collection.

Synopsis (Statistical Methods)	**Sample size calculation** The surveillance program will attempt to collect data on all individuals exposed to ~~elafibranor anytime from the date of LMP through pregnancy outcome~~. However, pregnancy exposures are expected to be extremely rare. Given the expected rarity of pregnancy exposures to elafibranor, a formal sample size calculation is not applicable for this surveillance program. Instead, the study will adopt an approach, aiming to identify and collect data on all eligible cases.	**Sample size calculation** The surveillance program will attempt to collect data on all individuals exposed to **at least one dose of elafibranor at any time during pregnancy, or since 3 weeks prior to the conception (based on estimated LMP)**. However, pregnancy exposures are expected to be extremely rare. Given the expected rarity of pregnancy exposures to elafibranor, a formal sample size calculation is not applicable for this surveillance program. Instead, the study will adopt an approach, aiming to identify and collect data on all eligible cases.	Definition of exposure has been corrected throughout the protocol to align with the wording of inclusion criterion #1.
Section 2.2	In the European Union (EU), elafibranor is contraindicated during pregnancy as per the summary of product characteristics (SmPC). In the United States, the Food and Drug Administration (FDA) label indicates that elafibranor is not recommended during pregnancy due to the potential risk of fetal harm based on preclinical data. ~~Regarding lactation, it is unknown whether elafibranor or its metabolites are excreted in human milk. No information is available on its excretion in animal milk.~~ However, adverse events (AEs) were observed in offspring when elafibranor was administered to female rats during pregnancy ~~and lactation~~ at clinically relevant exposures. […] In case of pregnancy, treatment with elafibranor should be discontinued as per the SmPC. Healthcare providers should carefully consider these factors when advising participants of childbearing potential or those who are breastfeeding. It is crucial that HCPs and are regularly reminded of the current label information regarding pregnancy ~~and lactation~~. As a reminder, elafibranor use in pregnancy is not recommended as per the USPI and the United Kingdom-SPC, and is contraindicated as per the EU-SmPC [21,22].	In the European Union (EU), elafibranor is contraindicated during pregnancy as per the summary of product characteristics (SmPC). In the United States, the Food and Drug Administration (FDA) label indicates that elafibranor is not recommended during pregnancy due to the potential risk of fetal harm based on preclinical data. However, adverse events (AEs) were observed in offspring when elafibranor was administered to female rats during pregnancy at clinically relevant exposures. […] In case of pregnancy, treatment with elafibranor should be discontinued as per the SmPC. Healthcare providers should carefully consider these factors when advising participants of childbearing potential or those who are breastfeeding. It is crucial that HCPs and are regularly reminded of the current label information regarding pregnancy. As a reminder, elafibranor use in pregnancy is not recommended as per the USPI and the United Kingdom-SPC, and is contraindicated as per the EU-SmPC [21,22].	Protocol updated to remove lactation or any reference to it.
Section 3	To describe developmental outcomes in infants and children (up to 2 years of age) born to participants exposed to elafibranor during pregnancy ~~and/or lactation~~.	To describe developmental outcomes in infants and children (up to 2 years of age) born to participants exposed to elafibranor during pregnancy.	Protocol updated to remove lactation.

Section 3	• Changes in biochemical markers of cholestasis from ~~baseline (at the time of elafibranor initiation)~~ through pregnancy and postpartum: - ALP - Bilirubin - ALT - AST - GGT - Albumin - Bile acids - CPK - Lipid profile (including total cholesterol, low density lipoproteins, high density lipoprotein, and triglycerides).	• Changes in biochemical markers of cholestasis from **last available measurement before pregnancy** and through pregnancy and postpartum: - ALP - Bilirubin - ALT - AST - GGT - Albumin - Bile acids - CPK - Lipid profile (including total cholesterol, low density lipoproteins, high density lipoprotein, and triglycerides).	The word baseline has been removed and replaced by last available measurement before pregnancy which better translates the actual data collection.
Section 4	This is an international, multicenter, prospective noninterventional pregnancy surveillance program designed primarily to collect and describe comprehensive safety data from pregnancies and outcomes in participants with PBC having had an exposure to ~~elafibranor either during pregnancy or within 3 weeks prior to conception.~~ The present study protocol is not a recommendation to expose pregnancies to elafibranor. As this is a noninterventional study, the decision to prescribe the product must be taken prior to, and independently from the decision to enroll the participant, keeping in mind the local label restrictions regarding pregnancy. This decision should be made in accordance with routine/standard clinical practice at the investigational site. The clinical justification for prescribing any treatment should be recorded at the outset by the prescribing clinician, as should the medical decision to pursue treatment prescription once a pregnancy has been confirmed.	This is an international, multicenter, prospective noninterventional pregnancy surveillance program designed primarily to collect and describe comprehensive safety data from pregnancies and outcomes in participants with PBC having had an exposure to **at least one dose of elafibranor at any time during pregnancy, or since 3 weeks prior to the conception (based on estimated LMP).** The present study protocol is not a recommendation to expose pregnancies to elafibranor. As this is a noninterventional study, the decision to prescribe the product must be taken prior to, and independently from the decision to enroll the participant, keeping in mind the local label restrictions regarding pregnancy. This decision should be made in accordance with routine/standard clinical practice at the investigational site. The clinical justification for prescribing any treatment should be recorded at the outset by the prescribing clinician, as should the medical decision to pursue treatment prescription once a pregnancy has been confirmed.	Definition of exposure has been corrected throughout the protocol to align with the wording of inclusion criterion #1.

Section 4.1	Following the United States FDA and Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approvals of the study protocol, participants will be enrolled, and data will be collected. The study is scheduled to be conducted with a planned end date of 2037. Participant follow-up will begin at the time of pregnancy identification in women exposed to at least one dose of elafibranor at any time ~~from the date of last menstrual period (LMP) through the pregnancy outcome~~. This follow-up will also include women who become pregnant within 3 weeks after discontinuing elafibranor, to account for the drug's half-life and potential residual effects. […] ~~The same data collection forms will be used for all participants, regardless of how they entered the study.~~ For enrolled participants, participation is voluntary, and these participants retain the right to withdraw their consent at any time. […] To ensure a comprehensive understanding of the impact of elafibranor exposure in pregnancy, the program will also incorporate relevant data from published clinical studies and literature regarding maternal, fetal and infant outcomes associated with exposure to at least one dose of elafibranor at any time during pregnancy, or since 3 weeks prior to ~~their LMP, or within 3 weeks of elafibranor discontinuation.~~ This additional data integration does not require formal enrollment or additional data collection from the sources.	Following the United States FDA and Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approvals of the study protocol, participants will be enrolled, and data will be collected. The study is scheduled to be conducted with a planned end date of 2037. Participant follow-up will begin at the time of pregnancy identification in women exposed to at least one dose of elafibranor at any time **during pregnancy, or since 3 weeks prior to the conception (based on estimated LMP).** This follow-up will also include women who become pregnant within 3 weeks after discontinuing elafibranor, to account for the drug's half-life and potential residual effects. […] For enrolled participants, participation is voluntary, and these participants retain the right to withdraw their consent at any time. […] To ensure a comprehensive understanding of the impact of elafibranor exposure in pregnancy, the program will also incorporate relevant data from published clinical studies and literature regarding maternal, fetal and infant outcomes associated with exposure to at least one dose of elafibranor at any time during pregnancy, or since 3 weeks prior to **the conception (based on estimated LMP).** This additional data integration does not require formal enrollment or additional data collection from the sources.	Definition of exposure has been corrected throughout the protocol to align with the wording of inclusion criterion #1. The word baseline has been removed and replaced by last available measurement before pregnancy which better translates the actual data collection.
Section 4.2	The elafibranor pregnancy surveillance program will aim to collect data on individuals who are exposed to at least one dose of elafibranor at any time during pregnancy, or since 3 weeks prior to ~~their LMP, or within 3 weeks of elafibranor discontinuation~~. While specific enrollment targets are not set due to the anticipated rarity of cases, the program will strive to gather data on as many pregnancies as possible to ensure an assessment of potential risks. This includes exposures across different trimesters and varying durations of elafibranor use. To be enrolled in the program, participants must meet all inclusion criteria (detailed in Section 5.1) and not fall under any exclusion criteria (outlined in Section 5.2).	The elafibranor pregnancy surveillance program will aim to collect data on individuals who are exposed to at least one dose of elafibranor at any time during pregnancy, or since 3 weeks prior to **the conception (based on estimated LMP).** While specific enrollment targets are not set due to the anticipated rarity of cases, the program will strive to gather data on as many pregnancies as possible to ensure an assessment of potential risks. This includes exposures across different trimesters and varying durations of elafibranor use. To be enrolled in the program, participants must meet all inclusion criteria (detailed in Section 5.1) and not fall under any exclusion criteria (outlined in Section 5.2).	Definition of exposure has been corrected throughout the protocol to align with the wording of inclusion criterion #1.

Section 4.3.4	Data on PBC will be collected, including date of diagnosis, biochemical markers ALP, ALT, AST, bilirubin, serum bile acids), liver status (fibrosis/cirrhosis staging, transplant history), and participant-reported status of pruritus. These measures will be documented ~~at baseline (defined as the last available measurement prior to pregnancy)~~ and throughout the 2-year follow-up period, as available in real-world practice settings transplant. The study will document all maternal exposures during pregnancy, who are exposed to at least one dose of elafibranor at any time during pregnancy, or since 3 weeks prior to ~~their LMP, or within 3 weeks of elafibranor discontinuation~~ with a primary focus on elafibranor use but also including other treatment medications, and non-medicinal substances to comprehensively assess potential influences on pregnancy outcomes. Suspected period will include pregnancy exposure within five times their elimination half-life.	Data on PBC will be collected, including date of diagnosis, biochemical markers ALP, ALT, AST, bilirubin, serum bile acids), liver status (fibrosis/cirrhosis staging, transplant history), and participant-reported status of pruritus. These measures will be documented **from last available measurement before pregnancy** and throughout the 2-year follow-up period, as available in real-world practice settings transplant. The study will document all maternal exposures during pregnancy, who are exposed to at least one dose of elafibranor at any time during pregnancy, or since 3 weeks prior to **the conception (based on estimated LMP)** with a primary focus on elafibranor use but also including other treatment medications, and non-medicinal substances to comprehensively assess potential influences on pregnancy outcomes. Suspected period will include pregnancy exposure within five times their elimination half-life.	Definition of exposure has been corrected throughout the protocol to align with the wording of inclusion criterion #1. The word baseline has been removed and replaced by last available measurement before pregnancy which better translates the actual data collection.
Section 4.3.6	• Number of fetuses e.g., singleton, multiple (twin, triplets etc.) • Estimated date of delivery (EDD) and method of determination (i.e. LMP or ultrasound); if ultrasound-determined, timing of ultrasound (before 140/7, before 220/7, or at or after 220/7 gestational weeks). Information on regular prenatal check-up data, maternal health assessments, fetal growth and development markers, pregnancy-related complications (e.g., eclampsia, pre-eclampsia), and importantly, ultrasound ~~images~~ of fetal pregnancies. • Prenatal tests performed, including name of test (e.g. ultrasound, amniocentesis, maternal serum alpha-fetoprotein, chorionic villus sampling), type of test (diagnostic or screening), date of test, and results/findings (e.g. major and minor congenital malformations). • Medical history of known concurrent risk factors to pregnancy outcomes e.g. diabetes, obesity, alcohol use, prescription medications, substance abuse, cardiovascular disease, hypertension, hyperlipidemia, obstetric complication (e.g. eclampsia, pre-eclampsia premature delivery, and prior intrahepatic cholestasis of pregnancy).	• Number of fetuses e.g., singleton, multiple (twin, triplets etc.) • Estimated date of delivery (EDD) and method of determination (i.e. LMP or ultrasound); if ultrasound-determined, timing of ultrasound (before 140/7, before 220/7, or at or after 220/7 gestational weeks). Information on regular prenatal check-up data, maternal health assessments, fetal growth and development markers, pregnancy-related complications (e.g., eclampsia, pre-eclampsia), and importantly, ultrasound **measurements** of fetal pregnancies. • Prenatal tests performed, including name of test (e.g. ultrasound, amniocentesis, maternal serum alpha-fetoprotein, chorionic villus sampling), type of test (diagnostic or screening), date of test, and results/findings (e.g. major and minor congenital malformations). • Medical history of known concurrent risk factors to pregnancy outcomes e.g. diabetes, obesity, alcohol use, prescription medications, substance abuse, cardiovascular disease, hypertension, hyperlipidemia, obstetric complication (e.g. eclampsia, pre-eclampsia premature delivery, and prior intrahepatic cholestasis of pregnancy).	Ultrasound data collection is done with measurements and not images.

Section 4.3.8	• To complement these postnatal data, the study will also incorporate results from anatomical scans performed during pregnancy, and in participants who are exposed to at least one dose of elafibranor at any time during pregnancy, or since 3 weeks prior to ~~their LMP, or within 3 weeks of elafibranor discontinuation~~. These prenatal imaging studies will provide valuable insights into fetal development, allowing for early detection of potential abnormalities and a more complete picture of fetal health throughout gestation.	• To complement these postnatal data, the study will also incorporate results from anatomical scans performed during pregnancy, and in participants who are exposed to at least one dose of elafibranor at any time during pregnancy, or since 3 weeks prior to **the conception (based on estimated LMP).** These prenatal imaging studies will provide valuable insights into fetal development, allowing for early detection of potential abnormalities and a more complete picture of fetal health throughout gestation.	Definition of exposure has been corrected throughout the protocol to align with the wording of inclusion criterion #1.
Section 4.4	For prospective cases, data collection occurs at enrollment, end of the second trimester, and pregnancy outcome, while retrospective cases provide all available data at enrollment. Follow-up begins at pregnancy identification for women who are exposed to at least one dose of elafibranor at any time during pregnancy, or since 3 weeks prior to ~~their LMP, or within 3 weeks of elafibranor discontinuation~~. For participants enrolled retrospectively (i.e. after the pregnancy outcome has occurred), the data collection process is tailored to capture existing information alongside ongoing infant development.	For prospective cases, data collection occurs at enrollment, end of the second trimester, and pregnancy outcome, while retrospective cases provide all available data at enrollment. Follow-up begins at pregnancy identification for women who are exposed to at least one dose of elafibranor at any time during pregnancy, or since 3 weeks prior to **the conception (based on estimated LMP).** For participants enrolled retrospectively (i.e. after the pregnancy outcome has occurred), the data collection process is tailored to capture existing information alongside ongoing infant development.	Definition of exposure has been corrected throughout the protocol to align with the wording of inclusion criterion #1.
Section 4.6	• Relevant data from any reports of pregnancy associated with exposure to elafibranor that are captured in the PV safety database e.g. through spontaneous reporting, reports of pregnancy identified during routine PV literature surveillance or reports of pregnancy from clinical trials, will be de-identified and shared with the pregnancy registry. Processes will be in place to identify any duplicate reporting from different sources.	• Relevant data from any reports of pregnancy associated with exposure to elafibranor that are captured in the PV safety database e.g. through spontaneous reporting, reports of pregnancy identified during routine PV literature surveillance or reports of pregnancy from clinical trials, will be de-identified and shared with the pregnancy registry. Processes will be in place to identify any duplicate reporting from different sources. **Data collection for these cases will occur as part of the routine PV follow-up process and will use forms which are similar to the study data collection forms.**	Clarification has been provided for cases captured through routine PV surveillance
Section 4.7	The study will be considered to have started when the first ~~participant has signed the informed consent (if applicable).~~ The study will be considered to have ended after the last participant and offspring data have been collected.	The study will be considered to have started when the first **virtual site has been initiated**. The study will be considered to have ended after the last participant and offspring data have been collected.	Corrected to align with operational aspects.

Section 6.1.2	• Changes in biochemical markers of cholestasis from ~~baseline (3 weeks prior to conception or at the time of elafibranor initiation)~~ through pregnancy and postpartum:	• Changes in biochemical markers of cholestasis from **last available measurement before pregnancy and** through pregnancy and postpartum:	The word baseline has been removed and replaced by last available measurement before pregnancy which better translates the actual data collection.
Section 6.1.5	• Complete physical examination assessment • Changes in vital signs (systolic and diastolic blood pressures and heart rate) from ~~baseline~~ through pregnancy and postpartum • Changes in safety lab parameters from ~~baseline~~ through pregnancy and postpartum.	• Complete physical examination assessment • Changes in vital signs (systolic and diastolic blood pressures and heart rate) from **last available measurement before pregnancy and** through pregnancy and postpartum • Changes in safety lab parameters from **last available measurement before pregnancy and** through pregnancy and postpartum.	The word baseline has been removed and replaced by last available measurement before pregnancy which better translates the actual data collection.
Section 7	This is a noninterventional study designed to characterize pregnancy and maternal complications and describe effects on the developing fetus, neonate and infant among individuals who are exposure to at least one dose of elafibranor at any time during pregnancy, or since 3 weeks prior to ~~their LMP, or within 3 weeks of elafibranor discontinuation~~. The decision to prescribe elafibranor will be made/was made prior to and independently of the decision to enroll the participant in this noninterventional study and should comply with the locally approved label.	This is a noninterventional study designed to characterize pregnancy and maternal complications and describe effects on the developing fetus, neonate and infant among individuals who are exposure to at least one dose of elafibranor at any time during pregnancy, or since 3 weeks prior to **the conception (based on estimated LMP)**. The decision to prescribe elafibranor will be made/was made prior to and independently of the decision to enroll the participant in this noninterventional study and should comply with the locally approved label.	Definition of exposure has been corrected throughout the protocol to align with the wording of inclusion criterion #1.
Section 8.4.3	- Specific Markers: The study will focus on key indicators of cholestasis and liver function, including serum bile acids, ALP, GGT, ALT, AST total bilirubin, CPK and lipid profile (including total cholesterol, LDL-C, HDL-C, VLDL-C, and triglycerides). For each parameter, actual values and change from ~~baseline~~ will be summarized using descriptive statistics.	- Specific Markers: The study will focus on key indicators of cholestasis and liver function, including serum bile acids, ALP, GGT, ALT, AST total bilirubin, CPK and lipid profile (including total cholesterol, LDL-C, HDL-C, VLDL-C, and triglycerides). For each parameter, actual values and change from **last available measurement before pregnancy** will be summarized using descriptive statistics.	The word baseline has been removed and replaced by last available measurement before pregnancy which better translates the actual data collection.

<table>
<tr>
<td>Section 9.2</td>
<td>Time Period and Frequency for Collecting and Reporting AE, SS and SAE Information
For the definition of the AEs and specials situation (SS), please refer to Section 9.1.</td>
<td>Time Period and Frequency for Collecting and Reporting AE, AESI, SS and SAE Information
For the definition of the AEs, AESI and specials situation (SS), please refer to Section 9.1.</td>
<td>AESI was added as missing in the title of this section and its body</td>
</tr>
<tr>
<td>Section 9.2.2</td>
<td>Health care practitioners must report to Ipsen PV all the following events using the “Adverse Event and Special Situation Reporting Form for noninterventional Studies” (134232-FOR):
• All SAEs – related and ~~non-~~related;
• All related nonserious AE/ADRs (Adverse Drug Reactions (ADRs));
• Any special situation (see definitions in Section 9.1).
<table>
<tr><th colspan="3">Primary Data Collection NIS</th></tr>
<tr><th>Safety Event</th><th>Collected on the CRF</th><th>Reported on the « AE NIS Form » to Ipsen Global Pharmacovigilance</th></tr>
<tr><td>Nonserious adverse event (AE)</td><td>All AEs related or not</td><td>Only the Related AEs - within 7 calendar days of awareness</td></tr>
<tr><td>Serious adverse event (SAE)</td><td>All SAEs related or not</td><td>All - within 24 hours of awareness</td></tr>
<tr><td>Special Situations (SS)</td><td>All SS related or not (regardless of whether associated with an AE)</td><td>All (regardless of whether associated with an AE) - within 7 calendar days of awareness</td></tr>
</table>
</td>
<td>Health care practitioners must report to Ipsen PV all the following events using the “Adverse Event and Special Situation Reporting Form for noninterventional Studies” (134232-FOR):
• All SAEs – related and not-related;
• All AESIs – related and not related;
• All related nonserious AE/ADRs (Adverse Drug Reactions (ADRs));
• Any special situation (see definitions in Section 9.1).
<table>
<tr><th colspan="3">Primary Data Collection NIS</th></tr>
<tr><th>Safety Event</th><th>Collected on the CRF</th><th>Reported on the « AE NIS Form » to Ipsen Global Pharmacovigilance</th></tr>
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<tr><td>Serious adverse event (SAE)</td><td>All SAEs related or not</td><td>All - within 24 hours of awareness</td></tr>
<tr><td>Adverse event of Special Interest (AESI)</td><td>All AESI related or not</td><td>All – within 24 hours of awareness</td></tr>
<tr><td>Special Situations (SS)</td><td>All SS related or not (regardless of whether associated with an AE)</td><td>All (regardless of whether associated with an AE) - within 7 calendar days of awareness</td></tr>
</table>
</td>
<td>Reporting instructions of AESI were missing in the section 9.2.2 although mentioned in the rest of the document.</td>
</tr>
<tr>
<td>Section 9.3</td>
<td>• The HCP will also consult the ~~HCP’s Brochure (IB) and/or~~ Product Information, for marketed products, in his/her assessment.
• For each AE/SAE, the HCP must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.</td>
<td>• The HCP will also consult the Product Information, for marketed products, in his/her assessment.
• For each AE/SAE, the HCP must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.</td>
<td>Reference to IB was removed as irrelevant here.</td>
</tr>
</table>

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LIST OF APPENDICES

Appendix 1 Congenital Malformation Coding References

MACDP Birth Defects Code List:

https://www.cdc.gov/ncbddd/birthdefects/documents/bpa-codes-rev2021-508c.xlsx

CDC List of Minor Congenital Malformations:

https://www.cdc.gov/ncbddd/birthdefects/surveillancemanual/appendices/appendix-b.html

Appendix 4: **European Registration of Congenital Anomalies and Twins Coding and Classification:**

https://eu-rd-platform.jrc.ec.europa.eu/system/files/public/JRC-EUROCATFull%20Guide%201%204%20version%2022-Nov-2021.pdf