SKYCLARYS® (Omaveloxolone) Pregnancy and Lactation Surveillance Program

Protocol 296FA402 (408-C-2303)

A post-marketing, observational, descriptive study to assess the risk of pregnancy and maternal complications and adverse effects on the developing fetus, neonate, and infant among individuals exposed to omaveloxolone during pregnancy and/or lactation

Study Phase:	IV
NDA Number:	216718
Indication:	Treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older
Investigator:	[redacted], PharmD, MPH [redacted] [redacted] 27560 Tel: [redacted]
Sponsor:	Reata Pharmaceuticals, Inc, a wholly owned subsidiary of Biogen.
Sponsor Contact Details:	225 Binney Street Cambridge, MA 02142 USA

Version	Date
1	14 June 2024

ABBREVIATIONS

Abbreviation	Definition
ACOG	American College of Obstetricians and Gynecologists
ADA	American Diabetes Association
AE	Adverse event
ART	Assisted reproductive technology
AUC	Area under the curve
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
DOC	Date of conception
EC	Ethics committee
EDD	Estimated date of delivery
EUROCAT	European Surveillance of Congenital Anomalies and Twins
FA	Friedreich's ataxia
FDA	Food and Drug Administration
FXN	Frataxin
GPP	Good Pharmacoepidemiology Practices
HCP	Healthcare provider
ID	Identification
INTERGROWTH-21st	International Fetal and Newborn Growth Consortium for the 21st Century
IRB	Institutional review board
LMP	Last menstrual period
MACDP	Metropolitan Atlanta Congenital Defects Program
MCM	Major congenital malformation
MSL	Medical science liaison
NVSS	National Vital Statistics System
PV	Pharmacovigilance
RHD	Recommended human dose
SAB	Spontaneous abortion
SAE	Serious adverse event
SGA	Small for gestational age
SOP	Standard operation procedure
STROBE	Strengthening the Reporting of Observational studies in Epidemiology
US	United States
USPI	United States Prescribing Information
VRCC	Virtual research coordination center
WHO	World Health Organization

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SYNOPSIS

Name of Sponsor: Reata Pharmaceuticals, Inc, a wholly owned subsidiary of Biogen
Name of Product: Omaveloxolone 50 mg capsules: SKYCLARYS®
Name of Active Ingredient: Omaveloxolone
Title of Study: SKYCLARYS (Omaveloxolone) Pregnancy and Lactation Surveillance Program: A post-marketing, observational, descriptive study to assess the risk of pregnancy and maternal complications and adverse effects on the developing fetus, neonate, and infant among individuals exposed to omaveloxolone during pregnancy and/or lactation
Study Number: 296FA402 (408-C-2303)
Phase of Development: IV
Clinical Sites: Worldwide reporting via a virtual research coordination center (VRCC)
Objectives: To assess risk of pregnancy and maternal complications and adverse effects on the developing fetus, neonate, and infant among individuals exposed to omaveloxolone during pregnancy and/or lactation.
Study Design: A phase IV prospective and retrospective study The SKYCLARYS (Omaveloxolone) Pregnancy and Lactation Surveillance Program is a post-marketing, worldwide, observational, descriptive study that collects prospective and retrospective data among individuals exposed to omaveloxolone during pregnancy and/or lactation. The study is designed to descriptively assess the association between omaveloxolone exposure during pregnancy and/or lactation and subsequent maternal, fetal, and infant outcomes. Cases reported during lactation only will be reported separately from pregnancy exposure cases. Participation in the surveillance program is voluntary, and participants who have given their consent can withdraw their consent to participate at any time. Data may be collected from enrolled pregnant or lactating individuals, or the healthcare providers (HCPs) involved in their care or the care of their infants, if applicable. The surveillance program is strictly observational; the schedule of office visits and all treatment regimens are determined by HCPs. No additional laboratory tests or HCP assessments will be required as part of this surveillance program. In addition, the surveillance program will incorporate cases from the global pharmacovigilance (PV) safety database including clinical studies, and published literature on maternal, fetal, and infant outcomes among individuals exposed to omaveloxolone during pregnancy and/or lactation. The design of this surveillance program follows current Food and Drug Administration (FDA) draft guidance for designing and implementing pregnancy safety studies [FDA 2019].

Enrollment/Data Collection:

To maximize participation and capture as many pregnancy and/or lactation exposures as possible, the surveillance program will allow multiple means of enrollment. Enrollment in the surveillance program may be accomplished as follows:

- Eligible pregnant or lactating individuals may self-enroll or be enrolled by their HCPs by providing informed consent and medical release(s) to the VRCC.
- Where applicable, HCPs may enroll pregnant or lactating individuals under an institutional review board (IRB)-/ethics committee (EC)-approved waiver of informed consent and provide de-identified data to the VRCC.

Enrolled pregnant or lactating individuals, and the HCPs involved in their care or the care of their infants, if applicable, will serve as data reporters to the surveillance program. If the participant is enrolled under an IRB-/EC-approved waiver of informed consent, the reporter who enrolled the participant will be responsible for providing all follow-up data to the surveillance program.

Participants enrolled prior to pregnancy outcome will be assessed throughout pregnancy, with data collection occurring at enrollment, at the end of the second trimester, at pregnancy outcome, and during lactation. For participants enrolled after the pregnancy outcome has occurred, all available pregnancy data will be collected at enrollment. Cumulative infant outcome data and maternal lactation information will be collected at approximately 4 months and 1 year of infant age, and data related to breastfeeding and maternal exposures during breastfeeding will be collected up to 1 year of infant age or weaning, whichever is first.

Number of Participants (Planned): All eligible individuals meeting the enrollment criteria will be considered for enrollment into the single-arm observational pregnancy safety study. As Friedreich's ataxia (FA) is a rare condition, approximately 10 to 20 individuals are anticipated to enroll during the study period.

Inclusion and Exclusion Criteria:

Each individual must meet the following inclusion criteria to be eligible for this study:

1. Exposure to at least 1 dose of omaveloxolone per label for FA at any time during pregnancy (from 12 days prior to conception to pregnancy outcome) and/or at any time during lactation (up to 1 year of infant age or weaning, whichever comes first) (see Section 8.3).
2. Informed consent or IRB-/EC-approved waiver of informed consent.

No exclusion criteria are defined.

Medicinal Product, Dosage, and Mode of Administration: SKYCLARYS (omaveloxolone) 150 mg (3 × 50 mg capsules) taken orally

Duration of Study: After approval of the protocol, enrollment of individuals in the surveillance program and data collection will commence. The study is planned to end not earlier than April 2035 with 10 years of data collection. Interim reports will be prepared annually, and a final report will be submitted upon completion.

For each prospectively enrolled individual, participation will begin at enrollment (during pregnancy) and end at pregnancy outcome (if fetal loss) or 1 year after pregnancy outcome (if live birth).

For each retrospectively enrolled individual, participation will begin after the pregnancy outcome has occurred and all available pregnancy data will be collected at enrollment. Individuals exposed during lactation only will be reported separately from pregnancy exposure cases.

Pharmacokinetic and Pharmacodynamic Assessments: None

Safety Assessments:

Primary outcome:

- Major congenital malformations

Secondary outcomes:

- Minor congenital malformations
- Gestational diabetes
- Preeclampsia
- Fetal loss
  - Spontaneous abortion (SAB)
  - Stillbirth
  - Elective or therapeutic abortion
  - Fetal loss, type not specified
- Live birth
- Preterm birth
- Small for gestational age
- Neonatal death
- Infant death
- Postnatal growth deficiency
- Infant developmental delay
- Infant hospitalization due to serious illness
- Infant serious or opportunistic infections

Statistical Methods:

The study population will include individuals who are exposed to at least 1 dose of omaveloxolone at any time during pregnancy (from 12 days prior to conception to pregnancy outcome) and/or lactation up through the first year following delivery.

The analysis population will include participants who:

- Are valid (i.e., meet the minimum criteria for enrollment [see Section 7.1] and are not a duplicate report)
- Are prospectively enrolled and were not exposed during lactation only
- Have HCP confirmation of data (i.e., do not have only patient-reported data)
- Have pregnancy outcome data or infant outcome data available (i.e., are not considered lost to follow-up)

This study is observational, and epidemiologic methods will be employed for data collection and analyses. Analyses will be conducted in accordance with the study objectives and applicable guidelines.

Study data will be summarized in tables and listings, as appropriate. These data include maternal demographic characteristics and pre-pregnancy anthropometrics, pregnancy information, maternal obstetrical history, family history of congenital malformations, disease information, maternal exposures during pregnancy, pregnancy outcome information (including gestational age of outcome), maternal lactation information and exposures during lactation (if applicable), and infant outcome information. For each continuous variable, the number of observations, median, mean, standard deviation, 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. Results will be rounded to 1 decimal place; therefore, percentages may not always add up to 100.

The incidence rates of the outcomes of interest in the analysis population will be calculated and reported. To put the surveillance program data into context, background rates from population-based surveillance systems and the published literature (e.g., Metropolitan Atlanta Congenital Defects Program [MACDP], National Vital Statistics System) will be referenced in the reports.

Demographic and baseline characteristics will be summarized for the entire enrolled population cumulatively and stratified by the following sub-populations, which are not mutually exclusive:

- Analysis population
- Participants prospectively enrolled in the lactation only study
- Retrospectively enrolled participants
- Prospectively enrolled participants lost to follow-up
- Participants with only patient-reported data

Sources of potential bias will be examined descriptively.

If sample size permits, subgroup analyses will be conducted within the analysis population considering:

- Timing (e.g., trimester of exposure)
- Extent of exposure (e.g., cumulative dose during pregnancy or lactation or relevant exposure window). Cases exposed during lactation only will be reported separately from pregnancy exposure cases and will not be part of the analysis population. See below for the description of supplementary analyses.
- Diagnostic prenatal test status prior to enrollment or first contact with the surveillance program
- Region (e.g., United States, Europe)

Although the descriptive analysis of the outcomes of interest will focus on the analysis population (i.e., prospectively enrolled participants with HCP-confirmed data), supplementary analyses will be conducted to descriptively summarize the outcome data collected for:

- Retrospectively enrolled participants
- Participants with only patient-reported data
- Participants exposed during lactation only

Clinical studies and published literature will be monitored yearly to identify reports of individuals exposed to omaveloxolone during pregnancy and/or lactation, and a summary of these reports will be included in each surveillance program report.

1. BACKGROUND AND RATIONALE

1.1. Omaveloxolone

SKYCLARYS® (omaveloxolone) is an Nrf2 activator that was approved in February 2023 by the United States (US) Food and Drug Administration (FDA) for the treatment of Friedreich's ataxia (FA) in adults and adolescents ages 16 years and older. The United States Prescribing Information (USPI) and patient package insert recommend that women who use hormonal birth control should use another form of birth control such as non-hormonal intrauterine system or an extra non-hormonal birth control such as condoms while using omaveloxolone and for 28 days after stopping omaveloxolone [SKYCLARYS® USPI 2024].

1.2. Potential Risks Associated with Exposure to Omaveloxolone During Pregnancy and/or Lactation

1.2.1. Animal Data

1.2.1.1. Pregnancy

Based on studies of omaveloxolone administered orally to rats and rabbits, there is potential for fetal harm and increased risk of developmental toxicity. In animal studies, administration of omaveloxolone during pregnancy or throughout pregnancy and lactation produced evidence of developmental toxicity (embryo-fetal mortality, growth impairment, and neurobehavioral deficits in offspring) at plasma exposures similar to or less than exposures in humans [SKYCLARYS® USPI 2024].

In a dose range-finding study, oral administration of omaveloxolone at doses up to 30 mg/kg/day to pregnant rats throughout organogenesis produced increases in post-implantation loss and resorptions, resulting in a decrease in viable fetuses and reduced fetal weight at the highest dose tested. However, in the pivotal study, oral administration of omaveloxolone (0, 1, 3, or 10 mg/kg/day) to pregnant rats throughout organogenesis resulted in no adverse effects on embryo-fetal development at any of the doses tested. At the highest dose tested in this study (10 mg/kg/day), plasma exposure (area under the curve [AUC]) was approximately 5 times that in humans at the recommended human dose (RHD) of 150 mg/day [SKYCLARYS® USPI 2024].

Oral administration of omaveloxolone (0, 3, 10, or 30 mg/kg/day) to pregnant rabbits throughout organogenesis resulted in increased post-implantation loss, decreased number of viable fetuses, decreased litter size, increased number of late resorptions, total resorptions (early and late), and decreased mean fetal body. No omaveloxolone-related fetal external, visceral, and skeletal malformations or developmental variations (external and visceral) were observed at the highest dose tested (30 mg/kg/day). In addition, lower male and female fetal body weights were observed at the 30-mg/kg/day omaveloxolone dose, which was associated with maternal toxicity. At the no-effect dose for adverse effects on embryo-fetal development (10 mg/kg/day), plasma exposure was less than that in humans at the RHD [SKYCLARYS® USPI 2024].

Oral administration of omaveloxolone (0, 1, 3, or 10 mg/kg/day) to rats throughout pregnancy and lactation resulted in an increase in stillbirths and impaired neurobehavioral function (increased locomotor activity and learning and memory deficits) in offspring at all doses;

reduced body weight in offspring at all but the lowest dose tested; delayed sexual maturation, manifested as an increased age of attaining preputial separation in males and decreased body weights of females at the time of vaginal opening; and increased postnatal mortality. No effect of treatment with omaveloxolone at the dose levels evaluated was observed on mating, fertility, or fecundity indices of the F_1 animals at the highest dose tested. A no-effect dose for adverse effects on pre- and postnatal development was not identified. Plasma exposure (AUC) at the lowest dose tested was less than that in humans at the RHD [SKYCLARYS® USPI 2024].

1.2.1.2. Lactation

There are currently no data on the presence of omaveloxolone or its metabolites in human milk. The effects on milk production and the breastfed infant are unknown. Omaveloxolone was excreted in the milk of lactating rats following oral administration. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for omaveloxolone and any potential adverse effects on the breastfed infant from omaveloxolone or from the underlying maternal condition [SKYCLARYS® USPI 2024].

1.2.2. Clinical Trial Data

There are no clinical studies of omaveloxolone in pregnant or lactating individuals, and no case reports on use of omaveloxolone during pregnancy or lactation in the post-marketing setting have been reported.

There are also no data available on the presence of omaveloxolone in human milk, the effects on breastfed infants, or the effects on milk production.

1.3. Friedreich's Ataxia in Pregnancy

1.3.1. Description and Epidemiology

Friedreich's ataxia is a rare, autosomal recessive, neurodegenerative disease with a prevalence of approximately 5,000 people in the US and 15,000 people worldwide. Studies suggest that FA is most observed in white populations, rare in sub-Saharan African populations [Koenig 1998; Labuda 2000], and rare in Japan. In a 2013 study, Vankan and colleagues synthesized available epidemiology studies that focused on different regions in Europe and concluded that approximately 2 in 100,000 people are affected by FA in Europe [Vankan 2013].

The most accurate way to diagnose FA through genetic testing and genetic family history [Schulz 2009]. After a patient begins showing symptoms that suggest a cerebellar ataxia, physicians generally will move on to genetic testing for the expanded GAA repeats in the frataxin (FXN) gene. FA has important negative consequences on life expectancy and quality of life. In terms of disease progression, early onset patients under 15 years of age usually become fully wheelchair dependent at a median of 11.5 years after the onset of first symptoms [Rummey 2020] with death occurring at a mean age of 39 years (standard deviation ± 14 years; range 13-73 years) [Indelicato 2024].

The hallmark neurological features of FA include progressive afferent and cerebellar ataxia, dysarthria, fixation instability, impaired vibration sense and proprioception, and pyramidal weakness. Most affected individuals have absent lower limb reflexes, but some have retained

reflexes and may have spasticity. Scoliosis, diabetes, foot deformity, and cardiomyopathy are common non-neurological features [Delatycki 1999; Dürr 1996; Schulz 2009]. Pathology related to FA includes degeneration of the dorsal root ganglia and posterior columns of the spinal cord, spino-cerebellar tracts, corticospinal tracts, dentate nuclei of the cerebellum, and the heart [Pandolfo 2003, 2009]. Since the discovery of the molecular basis underlying this disorder in 1996, there has been an abundance of studies exploring the nature of the mutation, the role of FXN, disease progression, and disease modifying agents [Forrest 1998; Pandolfo 2002; Puccio and Koenig 2000; Santos 2010].

1.3.2. Friedreich's Ataxia Pregnancy Outcomes

Limited data exist regarding the disease course of FA during pregnancy and potential adverse pregnancy outcomes. One retrospective study found no increased risk of spontaneous abortion, preeclampsia, or preterm birth among women with FA [Friedman 2010].

1.4. Study Rationale

The SKYCLARYS (Omaveloxolone) Pregnancy and Lactation Surveillance Program will add to the current body of knowledge regarding the safety of omaveloxolone exposure during pregnancy and/or lactation. Currently, there are no clinical studies of omaveloxolone in pregnant or lactating individuals and their offspring, and available human data on omaveloxolone exposure during pregnancy and/or lactation are insufficient to inform risk analysis. Data from the surveillance program will supplement data from animal toxicology studies and human exposure data. The goal of the surveillance program is to provide information on maternal, fetal, and infant outcomes following exposure to omaveloxolone during pregnancy and/or lactation, so that patients and physicians can weigh the benefits and risks of exposure to omaveloxolone during pregnancy and/or lactation and make informed treatment decisions.

2. STUDY OBJECTIVES AND OUTCOMES

2.1. Objectives

The objective of the SKYCLARYS (Omaveloxolone) Pregnancy and Lactation Surveillance Program is to assess risk of pregnancy and maternal complications and adverse effects on the developing fetus, neonate, and infant among individuals exposed to omaveloxolone during pregnancy and/or lactation. The prevalence rate of each of the outcomes of interest will be estimated among individuals exposed to at least 1 dose of omaveloxolone during pregnancy (from 12 days prior to conception to pregnancy outcome); the prevalence rate of infant outcomes will also be assessed among infants exposed to omaveloxolone through breastfeeding.

2.2. Outcomes

Primary and secondary outcomes are listed below. For information on the definitions and ascertainment of these outcomes, see Section 8.2.

Primary outcome:

- Major congenital malformations (MCM)

Secondary outcomes:

- Minor congenital malformations
- Gestational diabetes
- Preeclampsia
- Fetal loss
  - Spontaneous abortion (SAB)
  - Stillbirth
  - Elective or therapeutic abortion
  - Fetal loss, type not specified
- Live birth
- Preterm birth
- Small for gestational age (SGA)
- Neonatal death
- Infant death
- Postnatal growth deficiency
- Infant developmental delay
- Infant hospitalization due to serious illness
- Infant serious or opportunistic infections

3. STUDY DESIGN

3.1. Study Overview

The SKYCLARYS (Omaveloxolone) Pregnancy and Lactation Surveillance Program is a post-marketing, worldwide, observational, descriptive study that collects prospective and retrospective data among individuals exposed to omaveloxolone during pregnancy and/or lactation. The study is designed to descriptively assess the association between omaveloxolone exposure during pregnancy and/or lactation and subsequent maternal, fetal, and infant outcomes. Cases reported during lactation only will be reported separately from pregnancy exposure cases.

Participation in the surveillance program is voluntary, and participants who give consent to participate can withdraw their consent at any time. Data may be collected from enrolled pregnant or lactating individuals, or the healthcare providers (HCPs) involved in their care or the care of their infants, if applicable. The surveillance program is strictly observational; the schedule of office visits and all treatment regimens will be determined by HCPs. No additional laboratory tests or HCP assessments will be required as part of this surveillance program. The design of this surveillance program follows current FDA draft guidance for designing and implementing pregnancy safety studies [FDA 2019].

In addition, the surveillance program will incorporate cases from the global PV safety database including clinical studies and published literature on maternal, fetal, and infant outcomes among individuals exposed to omaveloxolone during pregnancy and/or lactation. See Section 10 for more information.

3.2. Study Duration and Follow-up

After FDA and institutional review board (IRB) approval of the protocol, enrollment of individuals in the surveillance program and data collection will commence. The study is planned to end no earlier than April 2035, with 10 years of data collection. Interim reports will be prepared annually, and a final report will be submitted upon completion. However, the study may be extended based on the achieved enrollment and follow-up of patients.

For each prospectively enrolled individual, participation will begin at enrollment (during pregnancy) and end at pregnancy outcome (if fetal loss) or 1 year after pregnancy outcome (if live birth).

For each retrospectively enrolled individual, participation will begin after the pregnancy outcome has occurred and all available pregnancy data will be collected at enrollment. Individuals exposed during lactation only will be reported separately from pregnancy exposure cases.

4. STUDY POPULATION

4.1. Participant Enrollment

To maximize participation and capture as many pregnancy and/or lactation exposures as possible, the surveillance program will allow multiple means of enrollment.

Enrollment in the surveillance program may be accomplished, as follows:

- Eligible pregnant or lactating individuals may self-enroll or be enrolled by their HCPs by providing informed consent and medical release(s) to the virtual research coordination center (VRCC; see Section 11.4.3).
- Where applicable, HCPs may enroll pregnant or lactating individuals under an IRB-/ethics committee (EC)-approved waiver of informed consent and provide de-identified data to the VRCC.

Pregnant or lactating individuals who are interested in participating may self-enroll in the surveillance program by calling the VRCC. To enroll, individuals will answer a series of screening questions designed to assess their eligibility and, if eligible, they will provide informed consent, their primary contact information, alternate contact information for a family member or friend outside of the household, contact information for HCPs who are/will be involved in their care or the care of their infants, and medical releases to allow these HCPs to provide data to the surveillance program.

HCPs may enroll pregnant or lactating individuals who they have identified in their practices and who meet eligibility criteria in the surveillance program with informed consent or under an IRB-/EC-approved waiver of informed consent. If the participant is enrolled under an IRB-/EC-approved waiver of informed consent, only de-identified data will be collected from the HCP. HCPs may refer individuals interested in self-enrolling to the VRCC or obtain consent and medical release(s) from the individuals directly. If an individual refuses to provide consent, no data (not even de-identified data) will be collected.

The surveillance program may collaborate with the existing registries/studies to identify individuals who have been exposed to omaveloxolone during pregnancy or lactation. The patients identified via existing registries/studies will be able to enroll in the surveillance program via the methods described above, based on their geographic location.

4.2. Study Population Enrollment Criteria

The study population will include individuals of any age who are exposed to at least 1 dose of omaveloxolone at any time during pregnancy and/or lactation.

4.2.1. Inclusion Criteria

Each individual must meet the following inclusion criteria to be eligible for this study:

- Exposure to at least 1 dose of omaveloxolone per label for FA at any time during pregnancy (from 12 days prior to conception to pregnancy outcome) and/or at any time during lactation (up to 1 year of infant age or weaning, whichever comes first).

- Informed consent or IRB-/EC-approved waiver of informed consent.

4.2.2. Exclusion Criteria

No exclusion criteria are defined.

4.2.3. Enrollment Criteria

The minimum criteria required for enrollment into the surveillance program are:

- Sufficient evidence to confirm that the individual is exposed to at least 1 dose of omaveloxolone per label for FA at any time during pregnancy or lactation
- Sufficient information to determine whether the participant is prospectively or retrospectively enrolled (i.e., whether the outcome of pregnancy occurred prior to first contact with the surveillance program)
- Full contact information for the reporter who enrolls the participant (i.e., pregnant or lactating individual, or HCP) to allow for follow-up

Participants without the minimum criteria for enrollment will be considered invalid and will not be included in the analysis population.

5. PARTICIPANT RECRUITMENT AND RETENTION

5.1. Recruitment Strategy

A targeted, multi-pronged recruitment campaign may be employed to recruit participants for the surveillance program. The campaign may target individuals who are pregnant or lactating, individuals using omaveloxolone, obstetric or pediatric HCPs, HCPs who are likely to treat FA, and HCPs who are likely to prescribe omaveloxolone. HCPs who are known to prescribe omaveloxolone may be identified using the Sponsor's distribution data or by medical science liaisons (MSLs). Obstetric HCPs and HCPs who are likely to treat FA may be identified using HCP directories and/or professional associations. Individuals who are pregnant or lactating and individuals using omaveloxolone may be identified using patient support groups and external data sources, such as pharmacy/medical claims or electronic medical records.

A multi-modal approach may be used to deliver surveillance program education and recruitment materials to targeted HCPs and patients. This approach involves direct-to-HCP outreach as well as online and print advertising directed to HCPs and patients. In addition, stakeholders who contact the Sponsor call center and may be eligible for participation will be referred to the VRCC.

Direct-to-HCP outreach may be achieved by delivering recruitment materials to targeted HCPs via e-mail, fax, and/or hardcopy mail. In addition, MSLs may provide surveillance program education and recruitment materials to HCPs in person. HCPs may be asked to identify potential surveillance program participants and encourage their participation by speaking to them about the surveillance program and providing them with the patient-directed surveillance program recruitment materials.

Information regarding the surveillance program may also be available on the following websites: PPD website (https://www.ppd.com/our-solutions/clinical/peri-and-post-approval/non-interventional-studies/pregnancy-and-lactation-studies/), the Sponsor's corporate website (https://www.biogen.com/), the FDA listing of pregnancy registries on www.fda.gov, www.clinicaltrials.gov, Society for Maternal-Fetal Medicine listing of registries (available to members via log-in), and the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance website (http://www.encepp.eu/). As deemed necessary, online advertisements on social media sites or other relevant websites (e.g., professional association websites or websites commonly visited by individuals who are pregnant or lactating) may be used to direct potential participants to the surveillance program.

Various print materials may also be used to provide information related to the surveillance program and facilitate recruitment. The SKYCLARYS product label and patient package insert will provide surveillance program information, including the surveillance program contact information. Information related to the surveillance program may also be directed to HCPs via announcements/publications in relevant professional journals/newsletters or presentations/exhibits at relevant professional meetings. As deemed necessary, print advertisements in newspapers or magazines with targeted patients among their readership may be used to direct potential participants to the surveillance program, and recruitment materials may be distributed to locations commonly frequented by targeted patients (e.g., ultrasound clinics, clinics that specialize in FA).

The success of the recruitment strategy will be monitored on an ongoing basis. Should additional efforts be required due to lower than anticipated enrollment, changes to the recruitment strategy will be considered at each interim report.

5.2. Retention Strategy

Retention will be facilitated by engaging surveillance program participants in the reporting process and minimizing the burden on reporters. Materials provided will emphasize the mission of the surveillance program to promote engagement and point readers toward the contact information for the program.

The VRCC will serve as the sole point of communication for participants and HCPs. The specialized staff, many of whom are obstetric nurses, have experience collecting data for observational studies from patients and research-naïve HCPs. They are experts at developing a rapport with HCPs and participants to facilitate data collection and build one-on-one relationships that will promote retention and reduce overall loss to follow-up.

The surveillance program will use streamlined data collection processes and simple, concise data collection forms that focus on endpoints of interest to reduce the burden of reporting. The surveillance program will provide multiple options for communication and data submission (e.g., phone, fax, mail, e-mail) and a flexible follow-up schedule to enhance retention and maximize data reporting. The surveillance program will also attempt to collect contact information of family members or friends outside of the household in case the participant cannot be reached, which can further promote retention.

To promote HCP engagement, study results may be shared with HCPs through various means (e.g., e-mail, newsletters).

6. DATA COLLECTION

6.1. Data Collection Process

Enrolled individuals and the HCPs involved in their care or the care of their infants, if applicable, will serve as data reporters to the surveillance program. If the participant is enrolled by an HCP under an IRB-/EC-approved waiver of informed consent, the HCP who enrolled the participant will be responsible for providing all follow-up data to the surveillance program. It is anticipated that most obstetric data will be collected (directly or via the reporter who enrolled the participant) from the participant's obstetric HCP, defined as any HCP who provides care during pregnancy (e.g., obstetrician, family practitioner, general practitioner); it is anticipated that most pediatric and lactation data will be collected (directly or via the reporter who enrolled the participant) from the infant's pediatric HCP, defined as any HCP who provides pediatric care (e.g., pediatrician, family practitioner, general practitioner). The surveillance program may also request data from other HCPs involved in the individual's or infant's care (e.g., prescriber, specialist) after appropriate medical release is obtained from the individual.

The data collection process for each participant enrolled prior to pregnancy outcome will begin at enrollment, and cumulative data throughout the pregnancy will be collected: at enrollment, at the end of the second trimester (approximately 26 gestational weeks), at pregnancy outcome (live birth or fetal loss), and during lactation. For participants enrolled after pregnancy outcome, all available pregnancy data will be collected at enrollment. For live-born infants, data will be collected at 2 timepoints: approximately 4 months and 1 year after delivery. Data collection forms are described below and will be identical for all enrolled participants regardless of their method of enrollment. Reporters to the surveillance program will use the data collection forms and will be instructed to transcribe data that are readily available in the patients' medical records into the data collection forms. If data are collected via telephone by the VRCC, the VRCC will complete the data collection forms.

Data collected at enrollment will be registration information (including eligibility criteria), maternal demographic characteristics, maternal pre-pregnancy anthropometrics, maternal obstetrical history, family history of congenital malformations, disease information, pregnancy information, and maternal exposures during pregnancy. These data will be collected on the ***Registration Form*** and ***Pregnancy Information Form***. Additionally, see Section 12.3.4 for reporting pregnancies on the ***Clinical Trial Pregnancy Notification and Outcome Form***. At approximately the end of the second trimester, the appropriate reporter will be asked to complete another ***Pregnancy Information Form***, which will collect any updates to pregnancy information and maternal exposures during pregnancy. Around or after the estimated date of delivery (EDD) or after a known pregnancy outcome, the appropriate reporter will be asked to complete another ***Pregnancy Information Form*** as well as the ***Pregnancy Outcome Form***, which will collect pregnancy outcome information (including gestational age at outcome) as well as any updates to pregnancy information and maternal exposures during pregnancy. Additionally, see Section 12.3.4 for reporting the outcome of pregnancies on the ***Clinical Trial Pregnancy Notification and Outcome Form***.

For each live-born infant, the appropriate reporter will be asked to complete an ***Infant Outcomes Form*** and ***Maternal Lactation Information Form***, which will collect infant information, including breastfeeding information, infant growth and development data, and maternal lactation

outcomes at 2 timepoints: approximately 4 months after delivery and approximately 1 year after delivery.

Data related to congenital malformations will be solicited at all data collection timepoints (at enrollment and throughout pregnancy on the ***Pregnancy Information Form,*** which collects data on prenatal testing, at pregnancy outcome on the ***Pregnancy Outcome Form***, and throughout the infant's first year of life on the ***Infant Outcomes Form***). If a congenital malformation (major or minor) or other event of interest is reported, additional information may be requested from the reporter on the ***Targeted Follow-up Form*** to properly characterize the event. Outcomes of pregnancies that meet serious adverse event (SAE) reporting requirements are included in Section 12.3.2. The date each data collection form is completed will also be collected. Table 1 provides 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. Section 6.1.1 provides further details regarding the data collected.

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, obstetric HCP, and prescriber, if needed Non-identifiable: HCP who enrolled participant	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 • Maternal exposures during pregnancy
Pregnancy Information Form	Identifiable: obstetric HCP and prescriber, if needed Non-identifiable: HCP who enrolled participant	Enrollment, end of second trimester[a], and EDD/pregnancy outcome[a]	• Ongoing pregnancy information • Maternal exposures during pregnancy
Pregnancy Outcome Form	Identifiable: obstetric HCP and pediatric HCP, if needed Non-identifiable: HCP who enrolled participant	EDD/pregnancy outcome	Pregnancy outcome information

Data Collection Form	Data Sources/Reporters	Timing of Completion, if Prospectively Enrolled	Data Collected
Maternal Lactation Information Form	Identifiable: participant, obstetric HCP, and pediatric HCP, if needed Non-identifiable: HCP who enrolled participant	Enrollment, approximately 4 months and 1 year after delivery	Maternal lactation information
Infant Outcomes Form	Identifiable: pediatric HCP Non-identifiable: HCP who enrolled participant	Approximately 4 months and 1 year after delivery	Breastfeeding information Infant outcome information
Targeted Follow-up Form	Identifiable: obstetric, pediatric, or other HCP Non-identifiable: HCP who enrolled participant	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.

6.1.1. Data Collected

6.1.1.1. Maternal Data

Registration Information

- Date of first contact with surveillance program
- Date of enrollment, defined as follows:
  - For participants who are self-enrolled and consented by the VRCC or participants who are enrolled and consented by their HCPs, date of enrollment is the date that informed consent is obtained
  - For participants who are enrolled under an IRB-/EC-approved waiver of informed consent and for whom only de-identified data are collected, date of enrollment is the date that the enrollment form is completed by the HCP
- Recruitment source(s)
- Minimum data for enrollment, including:
  - Pregnancy status
  - Omaveloxolone exposure information
  - Prior enrollment status

Maternal Demographic Characteristics

- Year of birth
- Country of residence
- Occupation

- Ethnicity
- Race

Maternal Pre-pregnancy Anthropometrics

- Pre-pregnancy anthropometrics (weight and height)

Maternal Obstetrical History

- Number of previous pregnancies, including multiple gestations
- Outcomes of previous pregnancies (SAB, stillbirth, elective or therapeutic abortion, live birth)
- Characteristics of previous live births (preterm, SGA)
- Number of previous fetuses/infants with congenital malformations (major and minor) and contributing factors

Family History of Congenital Malformations

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

Disease Information

- Maternal history of FA, including date of diagnosis
- Characteristics of FA, including Friedreich's Ataxia Rating Scale scores

Baseline Pregnancy Information

- First day of last menstrual period (LMP)
- Method of conception

Ongoing Pregnancy Information

- Number of fetuses
- EDD and method of determination (i.e., LMP, ultrasound, or assisted reproductive technology [ART] data); if ultrasound-determined, timing of ultrasound (before $14^{0/7}$, before $22^{0/7}$, or at or after $22^{0/7}$ gestational weeks)
- 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., congenital malformations)
- Concurrent maternal medical conditions, including:
  - Neurodegeneration
  - Cardiomyopathy
  - Thyroid abnormalities
  - Infectious diseases

  - Asthma
  - Diabetes
  - Hypertension
  - Seizure disorder
  - Autoimmune diseases
  - Depression and other psychiatric disorders
  - Hepatitis
  - Sexually transmitted diseases
  - Uterine or cervical abnormalities, including congenital uterine abnormalities
- Concurrent pregnancy-related maternal medical conditions or pregnancy complications, including:
  - Pregnancy-induced hypertension
  - Pre-eclampsia
  - Eclampsia
  - Gestational diabetes
  - Preterm labor
  - Placental abruption
  - Ectopic pregnancy

Maternal Exposures During Pregnancy

- Exposure to omaveloxolone, including indication/reason for use, dose, route, frequency, and dates/duration of exposure, if available
- Exposure to other drugs or products (including prescription and non-prescription drugs, dietary supplements, vaccines, known teratogens, and investigational medications), including indication/reason for use, dose, route, frequency, and dates/duration of exposure, if available
- Exposure to tobacco, alcohol, marijuana, or recreational or illicit drugs, including timing of exposure, if available

Pregnancy Outcome Information

- Pregnancy outcome, classified in 1 of the following mutually exclusive categories: fetal loss (SAB, stillbirth, elective or therapeutic abortion, or fetal loss, type not specified) or live birth
- Date of pregnancy outcome
- Gestational age at pregnancy outcome
- Fetal/infant sex

- Fetal/infant weight, length, and head circumference at pregnancy outcome
- Route of delivery (i.e., spontaneous vaginal delivery, assisted vaginal delivery, or cesarean delivery)
- Congenital malformations (major and minor) and assessment of potential contributing factors
- 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)
- For elective or therapeutic abortion, reason (e.g., finding on prenatal test, risk to mother's health, undesired pregnancy)

Maternal Lactation Information

- Cracked or sore skin at site of lactation, insufficient production of milk, breast engorgement, mastitis

6.1.1.2. Infant Data

Breastfeeding Information

- Breastfeeding information, including breastfeeding start/stop dates and maternal medicinal and recreational exposures during breastfeeding

Infant Outcome Information

- Infant weight, length, and head circumference at birth (if not provided at pregnancy outcome) and at approximately 4 months and 1 year of age
- Achievement of the developmental milestones in each category as defined by the US Centers for Disease Control and Prevention (CDC) (social/emotional, language/communication, cognitive, and movement/physical development) at approximately 4 months and 1 year of age
- Congenital malformations (major and minor) and assessment of potential contributing factors
- Infant death, including date and cause of death
- Infant illnesses and hospitalizations

Targeted Follow-up Information

- Details of the congenital malformations (major or minor) or other condition of interest
- Etiology
- Outcome attribution
- Specific questions requested by the Sponsor and/or the birth defect evaluator

6.1.2. Attempts to Obtain Follow-up Information

In the month that follow-up is due, the reporter will be contacted by the VRCC and asked to provide follow-up information. If needed, 3 subsequent attempts will be made approximately every 2 weeks via various modes of communication. If no response is received from the reporter, additional attempts may occur at the next planned data collection timepoint (e.g., at pregnancy outcome). When appropriate, the participant will be asked to encourage their HCP to provide the missing data. A final communication to obtain follow-up data will be sent via certified mail or an equivalent method indicating that the participant will be considered lost to follow-up if no further data are received. If, at any point in the follow-up process, the participant withdraws consent or the reporter indicates that the participant is lost to follow-up, no further attempts will be made. The reason the participant was lost to follow-up (e.g., no response from reporter, no response from participant, or participant withdrawal of consent) will be documented.

6.1.3. Follow-up Process for Clarification of Information

For critical data points (e.g., exposure and outcome data), if there are outstanding questions, discrepancies between forms, or missing data, the appropriate reporter will be contacted for clarification. If needed, 3 subsequent attempts will be made at intervals of approximately 2 weeks. If no further information is obtained, qualified program staff or the principal investigator will make a logical determination on discrepant information based on the available data. All clarifications and/or changes will be documented and traceable.

7. STUDY PARTICIPANT MANAGEMENT AND DISPOSITION

7.1. Valid Versus Invalid Participants

A valid participant is defined as an individual with sufficient data (i.e., the minimum criteria for enrollment; see Section 4.2) submitted to the surveillance program. Participants who lack the minimum data required for enrollment into the study will be considered invalid. Invalid participants will be enumerated in each surveillance program report but will not be included in the analysis population.

7.1.1. Duplicate Reports

With reports coming from multiple sources (i.e., pregnant or lactating individuals and HCPs), it is important to ensure that each case is counted only once [National Birth Defects Prevention Network (NBDPN) 2004]. Identification of duplicate reports may be problematic for the anonymously reported, de-identified cases where there is no specific identifying information. Reports received by the surveillance program will be reviewed for possible duplicate reporting. On receipt of a registration form, the report will be compared with other reports based on available data (e.g., age, LMP, EDD, and exposure information) to determine if the same report was received previously. If no duplication is identified, the report will be considered valid. If duplication is identified, the pregnancy reported earliest or the one with the most complete data will be maintained as the valid pregnancy and updated with any data from the other report not already captured. The duplicate report will be considered invalid, with the reason being "duplicate report."

7.2. Prospectively Enrolled Versus Retrospectively Enrolled Participants

The surveillance program will encourage prospective enrollment; however, retrospective enrollment in the surveillance program will be permitted. For participants exposed to omaveloxolone during both pregnancy and lactation, a prospectively enrolled participant is defined as an individual who is enrolled or for whom initial contact with the surveillance program is made prior to pregnancy outcome. For participants exposed during lactation only, data will be reported separately from pregnancy exposure cases and a prospectively enrolled participant is defined as an individual who is enrolled prior to the start of breastfeeding. For participants exposed to omaveloxolone during both pregnancy and lactation, 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 participants exposed during lactation only, data will be reported separately from pregnancy exposure cases and a retrospectively enrolled participant is defined as an individual who is enrolled following the start of breastfeeding. Retrospectively enrolled participants can be biased toward the reporting of more unusual and severe outcomes and are less likely to be representative of the general population than prospectively enrolled participants. Retrospectively enrolled participants and participants exposed during lactation only will be excluded from the analysis population and summarized separately in reports (see Section 9.2.1 and Section 9.2.2).

Diagnostic prenatal tests (e.g., ultrasound to scan for structural defects at approximately 20 gestational weeks, chorionic villus sampling, and amniocentesis) can determine with high accuracy whether a fetus has a structural or chromosomal abnormality. If the results of

diagnostic prenatal testing are known prior to enrollment or first contact with the surveillance program, regardless of the results, the individual will be considered prospectively enrolled. However, this practice may introduce bias due to knowledge or perceived knowledge (through diagnostic prenatal testing) of the pregnancy outcome [Gliklich 2020; Kennedy 2004]. If the sample size allows, 3 groups of prospectively enrolled participants will be examined in supplementary analyses:

- Individuals who are enrolled or for whom initial contact with the surveillance program is made prior to pregnancy outcome and prior to diagnostic prenatal testing (true prospective subgroup)
- Individuals who are enrolled or for whom initial contact with the surveillance program is made prior to pregnancy outcome but after diagnostic prenatal testing that did not indicate a fetal abnormality
- Individuals who were enrolled or for whom initial contact with the surveillance program is made prior to pregnancy outcome but after diagnostic prenatal testing that indicated a fetal abnormality

7.3. Participants Lost to Follow-up

A participant will be considered lost to follow-up if follow-up information is never obtained or is unavailable; pregnant individuals without pregnancy outcome information will be considered lost to follow-up, and live-born infants without follow-up data after birth will be considered lost to follow-up. See Section 6.1.2 for more information on the circumstances under which participants will be considered lost to follow-up. Participants who are lost to follow-up will be excluded from the analysis population, but their demographic and baseline characteristics will be summarized in the reports (see Section 9.2.1).

7.4. Participant with Only Patient-reported Data

If consent and medical release(s) are provided by the participant, the surveillance program will attempt to obtain HCP confirmation of all patient-reported data, including data provided by the participant at self-enrollment. Participants with only patient-reported data will be excluded from the analysis population, and patient-reported data without HCP confirmation will be summarized separately in the reports (see Section 9.2.1 and Section 9.2.2).

7.5. Subsequent Pregnancies

Individuals who have previously enrolled in the surveillance program with a prior pregnancy will be eligible to enroll in the surveillance program with subsequent pregnancies. Each pregnancy will be assigned a separate participant identification (ID) number, and the number of subsequent pregnancies will be enumerated in the reports.

7.6. Multiple Gestation Pregnancies

Multiple gestation pregnancies will be enrolled in the surveillance program and included in the analysis population; however, for the analyses of preterm birth, SGA, and postnatal growth

deficiency, multiple gestation pregnancies will be excluded from the analysis population due to the higher risk of these outcomes in twins and higher-order multiples (see Section 9.2.2.1).

7.7. Analysis Population

Individuals will be excluded from the analysis population if they are duplicate reports (invalid), they lack the minimum criteria for enrollment (invalid), the outcome of their pregnancy occurred prior to first contact with the surveillance program (retrospectively enrolled participants and participants exposed during lactation only), or if data are not confirmed by an HCP (participants with only patient-reported data). Participants with identifiable and non-identifiable data will be included in the analysis population if pregnancy outcome data are collected (i.e., the participant is not lost to follow-up).

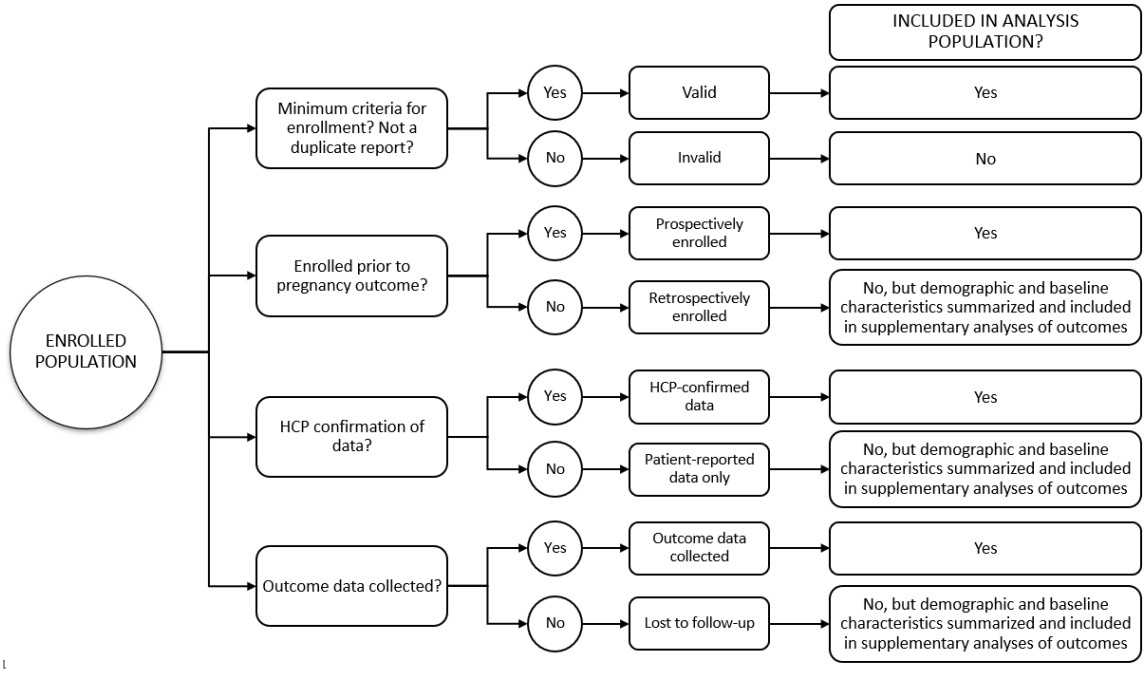
In summary, the analysis population will include participants who:

- Are valid
- Are prospectively enrolled and were not exposed during lactation only
- Have HCP confirmation of data
- Are not considered lost to follow-up

For the analyses of preterm birth, SGA, and postnatal growth deficiency, multiple gestation pregnancies will additionally be excluded from the analysis population (see Figure 1).

Retrospectively enrolled participants, participants exposed during lactation only, and participants with only patient-reported data will be included in supplementary analyses.

Figure 1. Summary of Analysis Population



HCP = healthcare provider.

8. DEFINITIONS OF VARIABLES

8.1. Exposure Definitions and Ascertainment

Exposure to omaveloxolone is a condition for enrollment. Exposure is defined as bodily uptake of at least 1 dose of omaveloxolone at any time during pregnancy (from conception to pregnancy outcome), prior to pregnancy (within a specified time based on the product's half-life), or during lactation. Due to the 57-hour half-life of omaveloxolone, participants will be considered exposed during pregnancy if a dose is taken within 12 days (5 half-lives) prior to conception. Participants will be considered exposed during lactation if a dose is taken at any time during lactation.

Detailed information on dose, route, frequency, dates/duration of exposure, and indication/reason for use will be collected, and exposure will be further categorized by earliest trimester of exposure. For information on the methods used to determine gestational age and trimester of exposure, refer to Section 8.3. Exposure information will be updated at each pregnancy and infant follow-up.

8.2. Outcome Definitions and Ascertainment

Table 2 presents the definitions of the outcomes. For outcomes not simply reported by the HCP, additional information on outcome ascertainment is provided.

Table 2. Outcome Definitions and Ascertainment

Outcome	Definition	Ascertainment
Major congenital malformation (MCM)	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 [Centers for Disease Control and Prevention (CDC) 2020]	The surveillance program defines and codes MCMs with criteria specified by CDC MACDP [Centers for Disease Control and Prevention (CDC) 2021]. If participants who reside in Europe are enrolled, MCMs will also be defined and coded using the criteria specified by EUROCAT [EUROCAT 2021]; APPENDIX A). 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 ovale, 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 [Holmes and Westgate 2011]. Adjudication process: An independent expert in clinical genetics and neonatology who is blinded to exposure 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. Then the birth defect evaluator will be unblinded to exposure and assess the possible temporal association between exposure (to omaveloxolone) and the development of the observed defects. If additional information is needed to aid in classification, the birth defect evaluator will request additional information using the targeted follow-up process outlined in Section 6.1.3. This evaluation will occur soon after the malformation is reported. Additional reviews will occur if new information is received for the case. The Sponsor will not be involved in any activities related to case review or adjudication.
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 [Centers for Disease Control and Prevention (CDC) 2020]	The surveillance program defines and codes minor congenital malformations with criteria specified as defined by CDC [Centers for Disease Control and Prevention (CDC) 2019]. The same process for adjudicating MCMs will be used to adjudicate minor congenital malformations.

Outcome	Definition	Ascertainment
Gestational diabetes	Any degree of glucose intolerance with onset or first recognition during pregnancy [American Diabetes Association 2004]	-
Preeclampsia	High blood pressure and signs of liver or kidney damage (e.g., proteinuria) occurring at >20 gestational weeks [ACOG Committee on Practice Bulletins--Obstetrics 2002]	-
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	Section 8.3 provides information on the methods used to calculate gestational age.
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 [American College of Obstetricians and Gynecologists (ACOG) 2020]	Section 8.3 provides information on the methods used to calculate gestational age.
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, type not specified	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	-
Preterm birth	A live birth occurring at <37 gestational weeks	Section 8.3 provides information on the methods used to calculate gestational age.

Outcome	Definition	Ascertainment
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 [Battaglia and Lubchenco 1967]	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 $24^{0/7}$ and $42^{6/7}$ gestational weeks [Villar 2014; Villar 2016]. 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 approximately 4 months and 1 year 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 World Health Organization (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 [Centers for Disease Control and Prevention (CDC) 2010].
Infant developmental delay	Failure to achieve the developmental milestones for chronological age, as defined by the CDC [Centers for Disease Control and Prevention (CDC) 2022]	Infant developmental delay will be evaluated at approximately 4 months and 12 years 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 visit due to a serious (i.e., results in significant disability, incapacity, or death; is life-threatening; requires inpatient or prolonged hospitalization; or is considered medically important) illness	-
Infant serious or opportunistic infections	An infection that occurs within an infant's first year of life and is either opportunistic (i.e., occurs more often or is more severe in people with weakened immune systems than in people with	-

Outcome	Definition	Ascertainment
	healthy immune systems) or serious (i.e., results in significant disability, incapacity, or death; is life-threatening; requires inpatient or prolonged hospitalization; or is considered medically important)	

ACOG = American College of Obstetricians and Gynecologists; ADA = American Diabetes Association; 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.

8.3. Other Variable Definitions and Ascertainment

Per the American College of Obstetricians and Gynecologists (ACOG), gestational age and the EDD should be determined by the obstetric HCP as soon as data are obtained on the LMP, first accurate ultrasound, or both. ACOG considers ultrasound measurement of the embryo or fetus in the first trimester (up to and including $13^{6/7}$ gestational weeks) the most accurate method to establish or confirm gestational age and discourages against changing the EDD based on subsequent ultrasounds. Any pregnancy without an ultrasound before $22^{0/7}$ gestational weeks to confirm or revise the EDD should be considered sub-optimally dated. If the pregnancy resulted from ART, the obstetric HCP should use ART-derived gestational age (e.g., based on age of embryo and date of transfer) to determine EDD. ACOG further recommends that the best estimate of EDD by the obstetric HCP, rather than estimates based on LMP alone, be used for research purposes [American College of Obstetricians and Gynecologists (ACOG) 2017].

Based on ACOG's recommendations, the surveillance program will attempt to collect the EDD from the obstetric HCP and determine whether the EDD was calculated based on LMP, ultrasound, or ART data. If ultrasound-based, whether the ultrasound was performed before $14^{0/7}$, before $22^{0/7}$, or at $22^{0/7}$ gestational weeks or later will also be collected. For prospectively enrolled participants, EDD data will be collected at each data collection timepoint throughout pregnancy. If a corrected EDD is reported on a subsequent form that is different from the EDD initially reported, the surveillance program will evaluate whether a correction is appropriate, based on the timing of the correction and the methods used to determine the corrected EDD, and follow-up with the reporter, if needed.

The surveillance program will conform to ACOG recommendations for determining the "best" EDD, and EDD will be used to calculate gestational age. Based on EDD, the first day of LMP and date of conception (DOC) will be calculated as follows:

- First day of LMP, defined as $0^{0/7}$ gestational week, will be calculated as EDD minus 280 days (40 weeks)
- DOC, defined as $2^{0/7}$ gestational weeks, will be calculated as first day of LMP plus 14 days (2 weeks)

If EDD is not reported by the HCP but LMP data are available, the surveillance program will use the first day of LMP to calculate EDD, gestational age, and DOC.

Gestational age will be calculated as the number of weeks elapsed since the first day of LMP.

- Gestational weeks $0^{0/7}$ to $13^{6/7}$ will be considered the first trimester
- Gestational weeks $14^{0/7}$ to $27^{6/7}$ will be considered the second trimester
- Gestational weeks $28^{0/7}$ to pregnancy outcome will be considered the third trimester

9. STATISTICAL METHODS AND SAMPLE SIZE

9.1. Sample Size

All eligible individuals meeting the enrollment criteria will be considered for enrollment into the single-arm, observational pregnancy safety study. As FA is a rare condition, and the USPI and patient package insert advise against using omaveloxolone during pregnancy or breastfeeding, approximately 10 to 20 individuals are anticipated to enroll during the study period.

9.2. Methods of Analysis

This study is observational, and epidemiologic methods will be employed for data collection and analyses. Analyses will be conducted in accordance with the study objectives and applicable guidelines.

Study data will be summarized in tables and listings, as appropriate (see Section 9.2.1 and Section 9.2.2 for more details). These data include maternal demographic characteristics and pre-pregnancy anthropometrics, pregnancy information, maternal obstetrical history, family history of congenital malformations, disease information, maternal exposures during pregnancy, pregnancy outcome information (including gestational age of outcome), maternal lactation information and exposures during lactation (if applicable), and infant outcome information. 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. Results will be rounded to 1 decimal place; therefore, percentages may not always add up to 100.

Data analyses will be performed with SAS® statistical software (version 9.4 or higher, SAS Institute, Cary, NC).

9.2.1. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized with simple descriptive statistics and presented in tables and listings. Demographic and baseline characteristics will be summarized for the entire enrolled population cumulatively and stratified by the following sub-populations, which are not mutually exclusive:

- Analysis population (see Section 7.7)
- Participants prospectively enrolled in the lactation only study
- Retrospectively enrolled participants
- Prospectively enrolled participants lost to follow-up
- Participants with only patient-reported data

9.2.2. Analysis of the Outcome Measures

The incidence rates of the outcomes of interest in the analysis population will be calculated and reported. Incidence rates of the outcomes of interest will be calculated as described in Section 9.2.2.1. To put the surveillance program data into context, background rates from

population-based surveillance systems and the published literature (e.g., Metropolitan Atlanta Congenital Defects Program [MACDP], National Vital Statistics System [NVSS]) will be referenced in the reports. The most current background rates at the time of reporting will be used.

Sources of potential bias will be examined descriptively, as described in Section 9.2.4.

If sample size permits, subgroup analyses will be conducted within the analysis population, considering the following:

- Timing (e.g., trimester of exposure)
- Extent of exposure (e.g., cumulative dose during pregnancy or lactation or relevant exposure window). Cases exposed during lactation only will be reported separately from pregnancy exposure cases and will not be part of the analysis population (see Section 7.7). See below for the description of supplementary analyses.
- Diagnostic prenatal test status prior to enrollment or first contact with the surveillance program (see Section 7.2)
- Region (e.g., US, Europe)

Although the descriptive analysis of the outcomes of interest will focus on the analysis population, supplementary analyses will be conducted to descriptively summarize the outcome data collected for:

- Retrospectively enrolled participants
- Participants with only patient-reported data
- Participants exposed during lactation only

9.2.2.1. Calculation of Outcome Prevalence

Incidence rates of the outcomes of interest will be calculated according to the conventions described in Table 3. In general, 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. 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 [Mason 2005].

For most outcomes, the denominator will be the number of pregnant individuals with pregnancy outcome data, the number of live births, or the number of infants with follow-up data at the timepoint of interest, as appropriate; however, for some outcomes, the denominator will be restricted based on certain relevant factors:

- For MCM, prevalence will be calculated among the subset of individuals who are exposed during the first trimester.
- For preterm birth, SGA, and postnatal growth deficiency, prevalence will be calculated among singleton live births due to the higher risk of these outcomes in twins and higher-order multiples.
- For live birth and infant outcomes (i.e., preterm birth, SGA, neonatal death, infant death, postnatal growth deficiency, infant developmental delay, infant serious or

opportunistic infections, and infant hospitalization due to serious illness), prevalence will be calculated among live births/infants without MCMs.

- For postnatal growth deficiency, infants born preterm or SGA will be excluded from the denominator.
- For infant developmental delay, infants born preterm will be excluded from the denominator.
- For infant hospitalization due to serious illness, infants born preterm will be excluded from the denominator.
- For SAB and preterm birth, prevalence will be calculated among the subset of individuals who are enrolled in the surveillance program prior to 20 and 37 gestational weeks, respectively.
- For some outcomes, prevalence will be calculated at multiple timepoints. For example, postnatal growth deficiency and infant developmental delay will be assessed at approximately 4 months and 1 year of infant age. At each timepoint, prevalence will be calculated among infants with data available for the particular outcome at that timepoint.

For the calculation of MCM prevalence rate, live births and stillbirths will be included in the numerator, and only live births will be included in the denominator. The MACDP calculates rates by this convention, which increases sensitivity [Correa 2007]. In the primary analysis, MCMs not associated with medication exposure will be included in the numerator; in the secondary analysis, they will be excluded.

Table 3. Calculation of Outcome Prevalence

Outcome	Numerator	Denominator
Primary analysis	Live births and stillbirths with confirmed MCMs (including MCMs not associated with medication exposure) among individuals with pregnancy outcome data and exposure during the first trimester	Live births among individuals with pregnancy outcome data and exposure during the first trimester
Secondary analysis	Live births and stillbirths with confirmed MCMs (excluding MCMs not associated with medication exposure) among individuals with pregnancy outcome data and exposure during the first trimester	Live births among individuals with pregnancy outcome data and exposure during the first trimester
Minor congenital malformations	Live births with minor congenital malformations among individuals with pregnancy outcome data	Live births among individuals with pregnancy outcome data
Gestational diabetes	Gestational diabetes among individuals with pregnancy outcome data	Individuals with pregnancy outcome data
Preeclampsia	Pre-eclampsia among individuals with pregnancy outcome data	Individuals with pregnancy outcome data

Outcome	Numerator	Denominator
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
Preterm birth	Singleton preterm live births without MCMs among individuals with pregnancy outcome data who are enrolled and exposed prior to 37 gestational weeks	Singleton live births without MCMs among individuals with pregnancy outcome data who are enrolled and exposed prior to 37 gestational weeks
SGA	Singleton live births without MCMs who are SGA based on weight among individuals with pregnancy outcome data	Singleton live births without MCMs with weight data among individuals with pregnancy outcome data
Postnatal growth deficiency (at approximately 4 months and 1 year)	Singleton infants without MCMs who were not born preterm, SGA with postnatal growth deficiency based on weight among infants with weight data at the timepoint	Singleton infants without MCMs who were not born preterm, SGA with weight data at the timepoint
Infant developmental delay (at approximately 4 months and 1 year)	Infants without MCMs who were not born preterm with developmental delay in a particular category among infants with developmental milestone data for the category at the timepoint	Infants without MCMs who were not born preterm with developmental milestone data for the category at the timepoint
Infant hospitalization due to serious illness	Infants without MCMs who were not born preterm, with a qualifying hospitalization from birth to 1 year of age among infants with hospitalization data up to 1 year of age	Infants without MCMs who were not born preterm with hospitalization data up to 1 year of age
Serious or opportunistic infant infection	Infants with a qualifying infection from birth to 1 year of age among infants with infection data up to 1 year of age	Infants with infection data up to 1 year of age

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

9.2.3. Missing Data

As described in Section 6.1.2, the surveillance program will make multiple attempts to obtain missing data for critical data points (e.g., exposure and outcome data). The frequency and percentage of participants with missing data for each data point will be presented. Missing data will not be imputed, with 1 exception. For start and end dates of medical conditions or exposures, if month and year are known but day is missing, day will be imputed for analyses; however, listings will continue to present the day as missing. Missing start dates will be set to the first day of the month, and missing end dates will be set to the last day of the month.

9.2.4. Limitations of the Research Methods and Statistical Considerations

The general limitations of pregnancy studies with voluntary participation are well known, and this study will not be an exception. One key limitation of the study is the small size of the population of pregnant or lactating individuals expected to be exposed to omaveloxolone during pregnancy or lactation.

This study is limited by the lack of an appropriate comparator group. Due to the rarity of this disease, the limited number of pregnancies expected among patients, and the high proportion of patients estimated to seek treatment with omaveloxolone, it is not expected that enrollment of an adequately sized untreated comparator group could be achieved in this study. To put the surveillance program data into context, background rates from population-based surveillance systems and the published literature (e.g., MACDP and NVSS) will be referenced in the reports. There are limitations to referencing the study results to risk estimates from a population-based surveillance system, including non-comparable geographic location and distribution (e.g., MACDP is drawn from the metropolitan Atlanta area), non-comparable demographic distributions and genetic composition, and the inability to discern the effects of omaveloxolone exposure from the effects of the underlying disease because comparator risk estimates are calculated in the general mostly healthy population.

Additionally, individuals enrolled in the surveillance program may differ from those in the general population in important factors that could affect pregnancy outcomes. Although it will not be possible to address imbalances (i.e., control for confounding) in the analysis, sources of potential bias will be examined and considered in the interpretation of study results.

Since participation in the surveillance program is voluntary, the individuals who are enrolled in the surveillance program may not be representative of the overall population of individuals who are pregnant or lactating. This could introduce selection bias and affect the generalizability of the results. To minimize the potential for selection bias, a multi-faceted recruitment strategy will be employed, individuals will be enrolled via multiple methods, and data will be collected from multiple sources.

Because the surveillance program will enroll individuals only after recognition of pregnancy and in some cases much later in pregnancy, there will be left truncation of the enrolled population. That is, the enrolled population of pregnant individuals will include individuals with a shortened period at risk of the outcomes of interest and will exclude individuals who have already had certain outcomes (e.g., SAB, elective or therapeutic abortion). To minimize the impact of this potential bias, the surveillance program's recruitment strategy will encourage recruitment of participants as early in pregnancy as possible. Since the analysis of surveillance program data is

focused on prospective enrollment, misclassification of drug exposure is non-differential with regard to outcome. However, outcome misclassification could occur especially with regard to minor congenital malformations that may be overlooked or unreported. Although some malformations may not be easily visible at birth, most will be apparent by 1 year of age, so misclassification of these outcomes is expected to be minimal in this surveillance program, which aims to follow infants through 1 year of age.

Pregnancies that result in fetal losses (stillbirths, SABs, and elective or therapeutic abortions) without reported MCMs may introduce a classification bias. The percentage of these pregnancies consisting of potentially normal outcomes or MCMs is unknown. The surveillance program's data collection forms attempt to obtain information on MCMs detected via prenatal testing and at the time of the outcome. However, the reporting physician may not know the condition of the lost fetus.

Finally, it is possible that outcomes among pregnant individuals and infants who are lost to follow-up could differ from those with documented outcomes. Because of differences in individual reporting patterns, it is not possible to assess with any certainty what impact the potential biases from the losses to follow-up may have on the analysis. However, the characteristics of those participants considered lost to follow-up will be descriptively compared with those in the analysis population in an attempt to address this potential source of bias.

The combined impact that potential biases will have on the study results is unknown, but each source of potential bias will be examined and discussed in the reports.

10. DATA FROM OTHER SOURCES

To allow for a comprehensive review of all reported pregnancy exposures, without requiring enrollment and further data collection, the surveillance program will incorporate cases from the global pharmacovigilance (PV) safety database including clinical studies, and published literature on maternal, fetal, and infant outcomes among individuals exposed to omaveloxolone during pregnancy and/or lactation. Review of the published literature, global PV database, and clinical study results will be conducted annually, and a summary of these reports will be included in each surveillance program report.

Similar to retrospectively enrolled participants, pregnancy exposure reports from other sources, such as clinical studies and published literature, may be biased toward the reporting of more abnormal outcomes and are less likely to be representative of the general population. It is inappropriate to calculate incidence rates from these reports; however, these reports may be helpful in the detection of possible signals and/or patterns of MCMs and other outcomes suggestive of common etiology.

The surveillance program will continually monitor clinical studies and published literature to identify reports of individuals exposed to omaveloxolone during pregnancy and/or lactation, and a brief summary of each report will be included in each surveillance program report.

11. PROTECTION OF HUMAN SUBJECTS

The Sponsor respects the participants' rights to privacy and will ensure the confidentiality of their medical information in accordance with applicable laws and regulations. Each participant's identity will be known only to the third-party contractor (PPD), the central surveillance program site (principal investigator, medical monitor, and VRCC), and the enrolling/participating individual (i.e., pregnant or lactating individual or HCP). At no time during the operation of the surveillance program will the Sponsor have access to personally identifiable information (with the exception of year of birth for safety reporting purposes) for any individual or any infant who has been enrolled in the surveillance program. The surveillance program will assign all individuals and infants ID numbers, which will be used to identify surveillance program participants and their infant offspring. The dataset used in each analysis of data from the surveillance program will contain coded surveillance program participant identifiers only for both the pregnant individuals and infants.

Each employee in the VRCC is fully trained in the protection of human subjects and data privacy and follows established standard operating procedures (SOPs) that outline specifically how to maintain confidentially of and data protection for all surveillance program participants. These SOPs also establish procedures should privacy be compromised in any way. The VRCC staff must train and test on these privacy SOPs annually.

11.1. Exemption of US Health Insurance Portability and Accountability Act Authorization

As a post-marketing safety reporting activity, this surveillance program meets the criteria in 45 Code of Federal Regulations (CFR)§164.512 for exemption from the US Health Insurance Portability and Accountability Act authorization.

11.2. Informed Consent

Informed consent will be obtained for each surveillance program participant who self-enrolls. As the research involves no more than minimal risk to the participants and involves no procedures for which written consent is normally required outside the research context, where allowed by local laws and regulations, adult participants will be given the option to provide verbal consent under the waiver of informed consent or signed informed consent. Adults are defined as individuals who have attained the legal age for consenting to treatments, procedures, or clinical investigations under applicable laws.

Minors are defined as individuals who have not attained the legal age for consenting to treatments, procedures, or clinical investigations under applicable law. This surveillance program will follow applicable laws for the country/state in which the participant resides. If a minor requests participation in the surveillance program and all eligibility criteria are met, the surveillance program will obtain assent from the minor and signed written consent from a parent or guardian.

At the initial screening with potential participants, the surveillance program associate will obtain consent to collect basic information about the individual, such as age and country/state of residence, to determine whether the individual is a minor and to ensure that applicable local laws and regulations are followed.

11.2.1. Additional Safeguards for Children in Clinical Investigations

Although this surveillance program involves the collection of information on infants after birth, the surveillance program protocol will be conducted in full consideration of all applicable laws and regulations. This surveillance program will ascertain maternal and infant information only via maternal and pediatric HCPs, and no clinical specimens will be collected from the infants; therefore, collection of data on infants of individuals in this surveillance program involves no greater than minimal risk to the infants. Although the infants will be too young to provide assent, the surveillance program protocol may request permission from the mothers, and they will be asked to provide authorization for release of medical information from their infants' HCPs.

11.2.2. Waiver of Informed Consent

As the research will involve no more than minimal risk to participants, where allowed by local law, a waiver of informed consent will be requested. If granted under appropriate IRB/EC approval, HCPs may report de-identified data to the surveillance program, under this waiver of informed consent. This approach is considered reasonable for the following reasons:

- **The waiver will not adversely affect the rights and welfare of the participants**. The privacy risks to individuals whose protected health information will be used or disclosed are reasonable in relation to the anticipated benefits to future patients and to the importance of the knowledge that may reasonably be expected to result from the research.
- **The research could not practicably be conducted without the waiver.** A critical component of a surveillance program such as this is the need to enroll a substantial number of participants to have the statistical power necessary to assess risk. To enroll as many patients as possible, this surveillance program seeks to accept enrollment via informed consent as well as enrollment under this waiver of informed consent.

11.3. Regulatory and Ethical Compliance

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) [ISPE 2015], with applicable local regulations and with the ethical principles laid down in the Declaration of Helsinki. The protocol will be submitted for approval to applicable regulatory authorities and IRB(s) prior to surveillance program implementation. The protocol, proposed waiver of documentation of informed consent, and proposed waiver of informed consent will be reviewed and approved by an IRB before study implementation. A signed and dated statement that the protocol and waivers have been approved by the IRB will be given to the Sponsor before study initiation. Prior to study start, the investigator will sign a protocol signature page confirming their agreement to conduct the study in accordance with these documents and all the instructions and procedures found in this protocol. If an inspection of the site is requested by a regulatory authority, the investigator must inform the Sponsor immediately that this request has been made.

11.4. Roles and Responsibilities of the Sponsor, Principal Investigator, and Research Coordination Center

The Sponsor, the principal investigator, and the VRCC will comply with this protocol and applicable regulations and ethical principles.

11.4.1. Sponsor

The Sponsor will provide financial support, general oversight, and decision-making for the surveillance program. The Sponsor may transfer any or all of its study-related responsibilities to a contract research organization and other third parties; however, the Sponsor retains overall accountability for these activities.

11.4.2. Principal Investigator

The principal investigator is responsible for providing oversight of the surveillance program and all submissions (protocol, amendments) to the IRB. The principal investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable regulations. The principal investigator will be available to the Sponsor for ongoing consultations regarding the review, analysis, and conduct of the surveillance program.

11.4.3. Virtual Research Coordination Center

The VRCC is responsible for assisting the principal investigator in all aspects of participant recruitment, informed consent, data collection, and management. As is noted in Section 11, the VRCC staff is fully trained on and compliant with SOPs regarding the protection of human subjects and data privacy.

12. MANAGEMENT AND REPORTING OF ADVERSE EVENTS AND PREGNANCIES

12.1. Definitions

12.1.1. Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Determination of whether an abnormal assessment (e.g., laboratory value, vital sign result, and/or electrocardiogram) result meets the definition of an AE will be made by the Investigator or HCP. Abnormal results are not considered AEs unless one or more of the following criteria are met:

- The result meets the criteria for an SAE.
- The result requires the participant to receive specific corrective therapy.
- The result is considered by the Investigator or HCP to be clinically significant.

12.1.2. Serious Adverse Event

An SAE in the surveillance program is any untoward medical occurrence related to pregnancy, pregnancy outcome and/or fetal, and infant outcomes (for outcomes see Section 2.2) after at least one dose:

- Results in death.
- In the view of the reporting HCP, places the participant or infant at immediate risk of death (a life-threatening event; however, this does not include an event that, had it occurred in a more severe form, might have caused death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is an important and significant medical event that, in the opinion of the reporting HCP, may jeopardize the participant or infant, or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home, which do not require an inpatient hospitalization.
- Is a pregnancy outcome of spontaneous abortion, fetal loss including stillbirth, ectopic pregnancy, elective or therapeutic pregnancy terminations, MCMs/congenital anomaly, premature births, SGA births, abnormal postnatal growth and development, or serious opportunistic infections.

- Obstetric complications that fall into these categories are defined as serious and should be reported to this surveillance program.

12.2. Safety Classifications

12.2.1. HCP Assessment of Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 12.1.2.
- The relationship of the event to omaveloxolone as defined in Section 12.2.2.
- The severity of the event as defined in Section 12.2.3.

12.2.2. Relationship of Events to Omaveloxolone

The following definitions should be considered when evaluating the relationship of SAEs to omaveloxolone:

Relationship of Event to Omaveloxolone Treatment	
Not related	An AE will be considered "not related" to the use of omaveloxolone if there is not a reasonable possibility that the event has been caused by omaveloxolone. Factors pointing toward this assessment include, but are not limited to, the lack of reasonable temporal relationship between administration of the product and the event, the presence of a biologically implausible relationship between the product and the AE (e.g., the event occurred before administration of the product), or the presence of a more likely alternative explanation for the AE.
Related	An AE will be considered "related" to the use of omaveloxolone if there is a possibility that the event may have been caused by omaveloxolone. Factors that point toward this assessment include, but are not limited to, a positive rechallenge, a reasonable temporal sequence between administration of the product and the event, a known response pattern of the suspected product, improvement after discontinuation or dose reduction, a biologically plausible relationship between the product and the AE, or a lack of an alternative explanation for the AE.

12.2.3. Severity of Events

The following definitions should be considered when evaluating the severity of SAEs:

Severity of Event	
Mild	Symptom(s) barely noticeable to participant or does not make participant uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s) but may be given.
Moderate	Symptom(s) of a sufficient severity to make participant uncomfortable; performance of daily activity is influenced; participant is able to continue in study; treatment for symptom(s) may be needed.
Severe	Symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on participant's daily life; severity may cause cessation of treatment with omaveloxolone; treatment for symptom(s) may be given and/or participant hospitalized.

12.3. Monitoring and Recording of Events and Pregnancies

12.3.1. Adverse Events

Nonserious AEs are not collected under the surveillance program and should be reported outside the surveillance program following standard PV practices. If the participant is enrolled in another study under the Sponsor of the surveillance program, reporting of nonserious AEs should follow that protocol.

12.3.2. Serious Adverse Events

Only SAEs related to pregnancy, pregnancy outcomes, and/or fetal and infant outcomes (for outcomes see Section 2.2) are required to be recorded under the surveillance program. HCPs will report SAEs under this surveillance program to the VRCC, and the VRCC will complete the SAE form and fax or email it to the Sponsor or designee within 24 hours of becoming aware of the SAE. Follow-up will be obtained as needed by the VRCC.

SAEs are to be reported on an SAE Form and recorded on the data collection forms from the time the participant enrolls until end at pregnancy outcome (if fetal loss) or 1 year after pregnancy outcome (if live birth) or premature study withdrawal, regardless of the event relationship to omaveloxolone.

Non-pregnancy-related SAEs should be reported outside the surveillance program following standard postmarketing PV practices. If the participant is enrolled in another study under the same Sponsor as the surveillance program, reporting of these SAEs should follow that protocol.

12.3.3. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded and reported as an SAE according to Section 12.3.2. The VRCC should make every effort to obtain and send death certificates and autopsy reports from the HCP. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

12.3.4. Reporting Pregnancy

For participants enrolled prior to pregnancy outcome, the Clinical Trial Pregnancy Notification and Outcome Form should be submitted to the Sponsor on 2 separate occasions:

1. The VRCC should send to the Sponsor or designee the initial report of pregnancy occurring in female participants, at the time of enrollment reported by the HCP, by faxing or emailing the Clinical Trial Pregnancy Notification and Outcome Form in addition to the data collection forms in Table 1.
2. The VRCC should send to the Sponsor or designee the outcome of the pregnancy by faxing or emailing the Clinical Trial Pregnancy Notification and Outcome Form and the data collection forms in Table 1.

For participants enrolled after pregnancy outcome, the VRCC should send the completed Clinical Trial Pregnancy Notification and Outcome Form and the data collection forms in Table 1 to the Sponsor or designee by fax or email.

Congenital abnormalities/birth defects in the offspring of the participants, ectopic pregnancies, spontaneous abortions and miscarriages, and stillbirths with or without fetal defects are considered to be SAEs and must be reported as such.

Normal and elective cesarean deliveries ("C-sections") performed for nonmedical reasons (i.e., scheduling, personal preference) and their related hospitalizations will not be considered SAEs, unless, in the view of the reporting HCP, the hospitalization was prolonged due to a complication.

12.3.5. Sponsor's Responsibilities

Sponsor's responsibilities include the following:

- Notify all appropriate regulatory authorities, IRB/ECs, and Investigators of SAEs, as required by local law, within required time frames.
- Expectedness of all SAEs will be determined by the Sponsor according to the approved local label.

13. ADMINISTRATIVE PROCEDURES

13.1. Quality Assurance

Ensuring that the data obtained and delivered to the Sponsor are of high quality will be an ongoing, multi-step process involving programming of edit checks for critical data variables in the electronic data capture system and visual review for completeness, logic, consistency, and accuracy. As is recommended in regulatory guidance documents, the data collection forms have been carefully designed to ensure data quality and integrity. Patient-reported data may be verified by the appropriate HCP. PPD will follow its SOPs as they relate to training of personnel, data handling, and processing, complying with 21 CFR Part 11 and GPP.

13.2. Study Funding

Reata Pharmaceuticals, Inc, a wholly owned subsidiary of Biogen, is the Sponsor of the study and is funding the study.

13.3. External Contract Organizations

PPD will be responsible for the conduct and administrative aspects of the study.

13.4. Study Closure

Study completion is planned for April 2035.

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

13.5. Study Reports and Publications

The surveillance program will produce interim study reports annually and a final comprehensive study report at the conclusion of the surveillance program. These reports will be submitted to the appropriate regulatory authorities. Abbreviated interim study reports will include a brief summary of the surveillance program design, methodology, a description of outreach and recruitment efforts, and results to date. The final report will include a comprehensive presentation of the surveillance program design, methodology, and results of the final biostatistical analysis along with an associated interpretive discussion of the surveillance program results. Interim and final 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 patient-reported data.

The data may also be considered for reporting at scientific conferences or for publication in scientific journals. Preparation of such manuscripts will be prepared in accordance with the Sponsor's SOPs and the current guidelines of STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) [STrengthening the Reporting of OBservational Studies in Epidemiology 2009].

13.6. Retention of Study Data

Investigators must retain all study records required by the Sponsor and by the applicable regulations in a secure and safe facility. The investigator must consult a Sponsor representative before disposal of any study records and must notify the Sponsor of any change in the location, disposition, or custody of the study files. Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced will be retained for a period of 5 years after close of the surveillance program in accordance with GPP guidelines. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution when these documents no longer need to be retained.

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15. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "SKYCLARYS® (Omaveloxolone) Pregnancy and Lactation Surveillance Program," and agree to conduct the study according to the protocol and the applicable guidelines and regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date

_____

Investigator's Name (Print)

16. APPENDIX A: 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

European Registration of Congenital Anomalies and Twins Coding and Classification:

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

17. APPENDIX B: SIGNATURES OF AGREEMENT FOR PROTOCOL

Study Title	SKYCLARYS® (Omaveloxolone) Pregnancy and Lactation Surveillance Program: a post-marketing, observational, descriptive study to assess the risk of pregnancy and maternal complications and adverse effects on the developing fetus, neonate, and infant among individuals exposed to omaveloxolone during pregnancy and/or lactation
Study Number	296FA402 (408-C-2303)

This clinical study protocol was subject to critical review and has been approved by Reata Pharmaceuticals, Inc, a wholly owned subsidiary of Biogen.

Signed: [redacted] Date: [redacted]