Non-Interventional Post Authorization Safety Study (PASS) Protocol

PRUCALOPRIDE PREGNANCY EXPOSURE STUDY: A VAMPSS POST-MARKETING SURVEILLANCE STUDY OF PRUCALOPRIDE SAFETY IN PREGNANCY

Compound:	Prucalopride
Study Type:	Phase 4/Non-Interventional Post Authorization Study
Protocol Number:	TAK-555-5001
Protocol Version	Version 4
Date of Issue:	12 January 2021
Study Director:	[redacted], M.S. [redacted], Safety Pharmacoepidemiology Global Evidence and Outcomes Takeda Pharmaceuticals [redacted]

PASS Information

US legal entity change for NDA and IND from Shire to Takeda was completed on 6 July 2020.

Title	Prucalopride Pregnancy Exposure Study: A VAMPSS Post-Marketing Surveillance Study of Prucalopride Safety in Pregnancy
Protocol version identifier	Version 4
Date of protocol	12 January 2021
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Medicinal product	Motegrity™
Product reference	Motegrity
Procedure number	N/A
Marketing authorization holder(s)	Takeda Development Center Americas, Inc. (TDC Americas) 95 Hayden Avenue Lexington, MA 02421 [redacted]
Joint PASS	No
Research question and objectives	Research question: "Is exposure to prucalopride therapy during pregnancy associated with increased risk of abnormal pregnancy or an adverse outcome to the baby?" The objective is to evaluate the potential effect of exposure to prucalopride in pregnancy compared with a group of disease-matched pregnant women who are not exposed to prucalopride. The primary outcome of the study is major structural defects, and the secondary outcomes of the study are spontaneous abortion, stillbirth, elective termination, neonatal/infant death, small for gestational age infants and small for age postnatal growth up to 1 year of age, and neurodevelopment, using the Ages in Stages Questionnaire, in live born infants up to 1 year of age
Country of the study	United States

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SIGNATURE PAGE

Motegrity Pregnancy Exposure Registry Protocol: TAK-555-5001

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LIST OF ABBREVIATIONS

AE	Adverse Event
AHRQ	Agency for Healthcare Research and Quality
ASQ	Ages and Stages Questionnaire
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CIC	Chronic Idiopathic Constipation
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FPI	First Patient In
GVP	Good Pharmacovigilance Practices
HIPAA	Health Insurance Portability and Accountability Act
IBS-C	Irritable Bowel Syndrome – Constipation
IPW	Inverse Probability Weighting
IRB	Institutional Review Board
LMP	Last Menstrual Period
MACDP	Metropolitan Atlanta Congenital Defects Program
MAH	Marketing Authorization Holder
NCHS	National Center for Health Statistics
OTIS	Organization of Teratology Information Specialists
PASS	Post-Authorization Safety Studies
PQI	Product Quality Issue
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedures
SSR	Special Situation Report
UCSD	University of California, San Diego
US	United States
VAMPSS	Vaccines and Medications in Pregnancy Surveillance System

1. RESPONSIBLE PARTIES

Principal Investigator	[redacted], PhD, MPH [redacted] Tel: [redacted] Email: [redacted]
Co-investigator	[redacted], MD [redacted]

2. ABSTRACT

Title: Prucalopride Pregnancy Exposure Study: A VAMPSS Post-Marketing Surveillance of Prucalopride Safety in Pregnancy

Background:

The Pregnancy Exposure Registry (the Registry) is sponsored by Takeda, is conducted by the Organization of Teratology Information Specialists (OTIS) Research Group, and is administered by investigators at the coordinating site located at the University of California, San Diego (UCSD).

This is a United States (US) based registry designed to monitor pregnancy and infant outcomes among women residing in the US exposed to prucalopride when used to treat the approved indication of chronic idiopathic constipation (CIC) as well as irritable bowel syndrome- constipation (IBS-C) in the cohort, and any indication in the exposure case series. Prucalopride has been approved in the US for the treatment of CIC. The Registry aims to fulfill a post-marketing requirement to the US Food and Drug Administration (FDA).

The goal of the Registry is to conduct an observational, controlled prospective cohort study that will involve follow-up of live born infants up to 1 year of age.

Research Question and Objectives:

Research Question: "Is exposure to prucalopride therapy during pregnancy associated with increased risk of abnormal pregnancy or an adverse outcome to the baby?"

To answer this research question, the investigators will monitor pregnancy and infant outcomes in women residing in the US exposed to prucalopride during pregnancy.

Objective: The objective of the study is to evaluate the potential effect of exposure to prucalopride in pregnancy compared with a comparison group of disease-matched pregnant women who are not exposed to prucalopride.

The primary outcome of the study is major structural defects in children up to 1 year of age.

The secondary outcomes of the study are rates of:

- Spontaneous abortion/miscarriage
- Stillbirth
- Elective termination/abortion
- Premature delivery
- Small for gestational age
- Postnatal growth of live born children up to 1 year of age
- Screening for neurodevelopmental milestones in children who are 1 year of age
- Hospitalization in live born children up to 1 year of age

Study Design:

This study will utilize a prospective, observational, exposure cohort design to examine pregnancy and infant outcomes in women and infants who are exposed to commercially supplied prucalopride during pregnancy to treat CIC or IBS-C. The prevalence of outcomes in women exposed to prucalopride and their infants will be compared with that observed in an unexposed disease-matched comparison group of women who have not used prucalopride during pregnancy. All participants will be recruited via voluntary participant registration following informed consent to participation by the pregnant woman. Subjects may withdraw from the study at any time.

Population:

The study population includes pregnant women who reside in the US who have or have not used prucalopride anytime in pregnancy for CIC or IBS-C.

Two groups of subjects will be enrolled and followed for pregnancy and infant outcomes:

- Pregnant women with CIC or IBS-C, exposed to prucalopride during pregnancy
- Pregnant women with CIC or IBS-C, not exposed to prucalopride during pregnancy

Variables:

Exposure will be defined as prucalopride treatment by maternal report, verified by medical record review, with detailed information on the gestational timing, route of administration, dose, and dates of exposure. Outcome variables include major structural defects, spontaneous abortion/miscarriage, stillbirth, elective termination/abortion, preterm delivery, infant birth size, postnatal growth of live born children up to 1 year of age, screening for neurodevelopmental milestones in children 1 year of age, and hospitalizations in live born children up to 1 year of age. These will be obtained by maternal report, and verified using medical records. Potential confounders or covariates to be collected include age, race/ethnicity, socioeconomic status, pregnancy and health history, lifestyle factors, comorbidities, medications, vaccine and vitamin/mineral exposures, prenatal tests, and measures of disease symptoms and severity. Details regarding definitions are provided in the Statistical Analysis Plan (SAP).

Data Sources:

Data will be collected using maternal interview(s), medical record reviews, and a pregnancy exposure diary. Maternal interview data will be recorded on hard copy forms, and medical record abstraction will be recorded on electronic forms. All records and forms will be retained by OTIS. Maternal interview forms are considered the primary data sources for the study. Data collected will be entered into a customized OTIS study database, located in the Research Center and developed specifically for the OTIS studies.

Study Size:

The cohort study target sample size is 616 pregnant women: 308 women who have been exposed to prucalopride in pregnancy for CIC or IBS-C, and 308 pregnant women diagnosed with CIC or IBS-C, who have not been exposed to prucalopride at any time in pregnancy, but who may or

may not have been exposed to an alternative treatment for the same indication. This sample size is sufficient to detect a 3-fold risk difference for major structural birth defects among pregnancies ending in at least one live-born infant, with a 2-sided alpha of 0.05% and 80% power. Up to an additional 100 women with exposure to prucalopride during pregnancy, but who do not meet the eligibility criteria for the cohort will be enrolled into the Registry Exposure Case Series. Although the Registry will follow-up on all pregnancies exposed to prucalopride (Registry Exposure Case Series), the core of the Registry will be a prospective, observational cohort study designed to ascertain and follow-up on pregnancy exposures to prucalopride that meet the eligibility criteria and to compare these to the above unexposed comparator group.

Data Analysis:

All relevant exposure, outcome, and covariate data within each study group will be summarized using descriptive statistics in each annual interim report. Means and standard deviations will be presented for continuous variables and frequencies and percentages will be presented for categorical variables. Statistical analysis will be performed at the completion of data collection.

Milestones:

The study is planned for 5.5 years from the enrollment of the first patient in (FPI) until study completion. There will be 3 years of active recruitment, with an annual interim report reviewed by the Scientific Advisory Board each year. The recruitment period will be re-evaluated annually to assess whether the recruitment window should be extended. The final report with statistical analysis according to the SAP will be prepared at the end of the study.

3. AMENDMENTS AND UPDATES

None

4. MILESTONES

Activity	**Timeline**
Start of data collection	First Quarter 2021
End of data collection	01 November 2025
Recruitment reports	Monthly Upon Start of Data Collection 2021 to December 2025
Annual reports	Annually Upon Start of Data Collection 2021 to 2026
Registration in the EU PAS register	N/A
Final study report	30 June 2026

5. RATIONALE AND BACKGROUND

Chronic constipation is a highly prevalent condition estimated to affect as many as 14% of the population, and is more common in women than men (Suares and Ford, 2011; Lembo and Camilleri, 2003). Prucalopride is an oral selective serotonin (5-HT) receptor agonist with enterokinetic properties that is currently approved in the US treat CIC in adults.

Prucalopride is a gastrointestinal prokinetic agent that stimulates colonic peristalsis which increases bowel motility. Its plasma termination half-life is estimated to be approximately 30 hours. The recommended dose of prucalopride is 2 mg per day in adult patients without severe renal impairment (Takeda Pharmaceuticals Company Limited, 2020).

As CIC occurs in women of reproductive age who may become pregnant, the safety profile of prucalopride in pregnancy is important to be established. Coadministration of prucalopride with an oral contraceptive in 13 nonpregnant female participants did not result in any clinically meaningful pharmacokinetic interactions suggesting that prucalopride is unlikely to reduce the effectiveness of oral contraceptives in women who are not planning pregnancy (Van de Velde et al., 2013).

5.1 Preclinical Studies with Prucalopride

In oral embryofetal development studies in rats and rabbits, prucalopride was administered to pregnant animals at doses of 5, 20, and 80 mg/kg/day throughout the period of organogenesis. No adverse embryofetal development effects were observed in either rats or rabbits up to the highest oral dose of 80 mg/kg/day (about 390 times and 780 times the recommended human dose of 2 mg/day, respectively, based on body surface area) (Takeda Pharmaceuticals Company Limited, 2020).

In an oral pre- and post-natal development study in rats, prucalopride was administered at doses of 5, 20, and 80 mg/kg/day. At the 80-mg/kg dose (about 390 times the recommended human dose of 2 mg/day, based on body surface area), a slight decrease in overall survival rate of pups after 7 days was observed, which could be due to maternal toxicity observed at this dose (Takeda Pharmaceuticals Company Limited, 2020).

5.2 Clinical Studies with Prucalopride

Available data from case reports with prucalopride use in pregnant women are insufficient to identify any drug-associated risks of miscarriage, major birth defects, or adverse maternal or fetal outcomes. Therefore, there is a need to conduct a pregnancy exposure study of pregnancy and infant outcomes with prenatal exposure to prucalopride (Takeda Pharmaceuticals Company Limited, 2020).

5.3 Pharmacoepidemiology Studies with Prucalopride

A pharmacoepidemiology study consisting of 3 substudies was conducted using data drawn from the Clinical Practice Research Dataset (CPRD) in the United Kingdom. The first substudy was designed as a drug utilization study to characterize a cohort of initiators of prucalopride. The

second substudy was designed to assess the incidence of selected cardiovascular events among initiators of prucalopride.

The third substudy was designed as a pregnancy surveillance analysis designed to characterize pregnancy outcomes in a cohort of women exposed to prucalopride during their pregnancy. No comparator group was included as part of the pregnancy surveillance substudy. Pregnancy exposure to prucalopride was defined as any prucalopride prescription within 45 days prior to the first pregnancy-specific record or during pregnancy. Pregnancy outcomes were classified as live birth, elective pregnancy termination, spontaneous abortion or still birth, and presence and type of major malformations determined based on Read codes and a general practitioner questionnaire. In the pregnancy surveillance substudy, 14 pregnancies in 12 women were classified as exposed to prucalopride, with all exposures occurring during the first trimester. Pregnancy outcomes consisted of 5 live births, 4 spontaneous abortions, 3 elective pregnancy terminations, and 2 indeterminate outcomes. No fetal malformations were identified (Study SHP555-804).

6. RESEARCH QUESTIONS AND OBJECTIVES

The purpose of the Prucalopride Pregnancy Exposure Registry is to evaluate the effect of prucalopride exposure on pregnancy and infant outcomes in exposed pregnancies compared with unexposed disease matched pregnancies. Limited human fetal safety data for prucalopride makes such a monitoring system an important component of epidemiologic research on the safety of this drug.

6.1 Objective

The objective of the study is to evaluate the potential effect of exposure to prucalopride in pregnancy compared with a comparison group of disease-matched pregnant women who are not exposed to prucalopride.

The primary outcome of the study is major structural defects in children up to 1 year of age.

The secondary outcomes of the study are rates of:

- Spontaneous abortion/miscarriage
- Stillbirth
- Elective termination/abortion
- Premature delivery
- Small for gestational age
- Postnatal growth of live born children up to 1 year of age
- Neurodevelopmental milestones in children at 1 year of age
- Hospitalization in live born children up to 1 year of age

7. RESEARCH METHODS

7.1 Study Design

This study will utilize a prospective, observational, exposure cohort design to examine pregnancy and infant outcomes in women and infants who are exposed to prucalopride during pregnancy to treat CIC or IBS-C. The prevalence of outcomes in women exposed to prucalopride and their infants will be compared with the prevalence observed in an unexposed disease-matched comparison group of women who have not used prucalopride during pregnancy but have been diagnosed with CIC or IBS-C. All subjects will be recruited via voluntary enrollment following informed consent to participate by the pregnant woman. Subjects may withdraw from the study at any time. Up to an additional 100 women with exposure to prucalopride during pregnancy, but who do not meet the eligibility criteria for the cohort will be enrolled into the Registry Exposure Case Series. Although the Registry will follow-up on all pregnancies exposed to prucalopride (Registry Exposure Case Series), the core of the Registry will be a prospective, observational cohort study designed to ascertain and follow-up on pregnancy exposures to prucalopride that meet the eligibility criteria and to compare these to the above unexposed comparator group.

7.2 Setting

The Registry study will be conducted by OTIS (Organization of Teratology Information Specialists), which is a network of university and health department based information centers serving pregnant women and healthcare providers throughout North America (Leen-Mitchell et al., 2000). These services receive spontaneous telephone and other forms of inquiries from women and healthcare providers about the safety or risk associated with environmental exposures in pregnancy, including medications. Trained Teratogen Information Specialists at each site provide appropriate risk assessment and referral for all patient and healthcare providers free of charge. These services also provide a basis for collaborative research such as this Registry. Thus, individual Teratogen Information Services located throughout the US and Canada will serve as a source of referrals of pregnant women residing in the US not only for prucalopride-exposed pregnancies but also for similarly ascertained disease-matched comparison pregnant women who have not used prucalopride in pregnancy.

Organization of Teratology Information Specialists member services receive over 70,000 teratogen information inquiries per year; therefore, OTIS members constitute a major source of identification and recruitment of exposed women and appropriate comparison women. Once women are in contact with the Registry Research Coordinating Center, enrollment in the Registry is voluntary and requires informed consent of the pregnant woman. The Registry encourages enrollment as early in the pregnancy as possible, before any prenatal testing results are known. This is accomplished by encouraging clinicians to refer patients, and patients who contact an OTIS service or who self-refer, to enroll upon first positive pregnancy test. These efforts reduce possible bias based on prior knowledge of a normal or abnormal ultrasound or other prenatal test, and allow for better estimation of risk of spontaneous abortion.

The study population includes pregnant women who reside in the US, with prucalopride-exposure for CIC or IBS-C and a comparison group with CIC or IBS-C without

prucalopride exposure during pregnancy (disease-matched unexposed comparison group). Based on use of multiple methods for identification and recruitment of exposed women, and the previous recruitment experience of the existing OTIS studies, the investigators have projected that approximately 103 pregnant women with exposure to prucalopride could be enrolled in the Registry each year, although the true number of exposed pregnancies potentially available for enrollment in the Registry cannot be known at this time.

7.3 Duration of the Study

The study is planned for 5.5 years from the enrollment of the FPI until study completion. There will be 3 years of active recruitment, with an annual interim report reviewed by the Scientific Advisory Board each year. The recruitment period will be evaluated annually to assess whether the recruitment period should be extended. The final report with statistical analysis will be prepared at the end of the study according to the SAP.

7.4 Eligibility Criteria

The prospective cohort study will enroll pregnant women in two cohorts.

7.4.1 Inclusion Criteria

Cohort 1: Prucalopride-Exposed Cohort

1. Pregnant women
2. Exposure to prucalopride for the treatment of CIC or IBS-C, for any number of days, at any dose, and at any time from the 1st day of the last menstrual period up to and including the 12th week after the first day of the last menstrual period (LMP). If the date of LMP is unclear, or if a first-trimester ultrasound has been done and the estimated date of conception is more than one week discrepant from the menstrual period calculation, the first-trimester ultrasound-derived date will be used to calculate a date for LMP and conception,
3. Agree to the conditions and requirements of the study including the interview schedule, and release of medical records

Cohort 2: Disease-Matched Comparison Cohort

1. Pregnant women
2. Diagnosed with CIC or IBS-C; frequency matched to the exposed group by disease indication, with the indication validated by medical records when possible
3. No exposure to prucalopride at any time in the current pregnancy; may or may not have taken another medication for their disease in the current pregnancy
4. Agree to the conditions and requirements of the study including the interview schedule, and release of medical records

7.4.2 Exclusion Criteria

Cohort 1: Prucalopride-Exposed Cohort

1. Women who have first contact with the project after prenatal diagnosis of any major structural defect
2. Women who have enrolled in the prucalopride cohort study with a previous pregnancy (women may only enroll once in the Prucalopride Pregnancy Cohort Study)
3. Women who have used prucalopride for an indication other than CIC or IBS-C
4. Women who do not have exposure in the first trimester of pregnancy
5. Retrospective enrollment after the outcome of pregnancy is known (ie, the pregnancy has ended prior to enrollment)
6. Results of a diagnostic test are positive for a major structural defect prior to enrollment. However, women who have had any normal or abnormal prenatal screening or diagnostic test prior to enrollment are eligible as long as the test result does not indicate a major structural defect.

Cohort 2: Disease-Matched Comparison Cohort (See Appendix 1 for diagnostic criteria)

1. Women who have first contact with the project after prenatal diagnosis of any major structural defect
2. Exposure to prucalopride anytime during the current pregnancy
3. Women who have enrolled in the prucalopride cohort study with a previous pregnancy (women may only enroll once in the Prucalopride Pregnancy Cohort Study)
4. Retrospective enrollment after the outcome of pregnancy is known (ie, the pregnancy has ended prior to enrollment)
5. Results of a diagnostic test are positive for a major structural defect prior to enrollment. However, women who have had any normal or abnormal prenatal screening or diagnostic test prior to enrollment are eligible as long as the test result does not indicate a major structural defect.

7.4.3 Prucalopride-Exposed Pregnancies Not Eligible for the Cohort Study

By study design, pregnancies that do not meet the prospective exposed cohort criteria for reasons described in Section 7.4.2 will be excluded from the cohort analysis; however, information on birth outcomes can be obtained and can be useful when reviewing the cohort data for any evidence of increased risks for the study outcomes. For this reason, women who do not meet the exposed cohort criteria will be invited to enroll in a separate “Exposure Case Series.” Women who are eligible for enrollment in the “Exposure Case Series” include, but are not limited to: 1) use of prucalopride in pregnancy for an unapproved indication other than IBS-C, 2) retrospective report of a prucalopride-exposed pregnancy after the outcome of pregnancy is known or results of a prenatal diagnostic test are positive for a major structural defect prior to enrollment, and 3) women with exposure to prucalopride who have enrolled in the prucalopride cohort study group previously. With informed consent, data will be collected from maternal

questionnaires and medical record review using the same protocol as the cohort study to the extent possible.

7.4.4 Analysis Populations

The Registry will collect and follow-up on reports of all types (ie, retrospective, exposure after first trimester only, indication other than CIC or IBS-C, etc: see Section 7.4.3) involving pregnancy exposure to prucalopride; however, the core of the Registry will be a prospective cohort study designed to ascertain and follow-up on first-trimester prospective reports of pregnancy exposures to prucalopride for CIC or IBS-C and will compare these outcomes with those of an internally generated comparison group consisting of diseased-matched pregnant women with CIC or IBS-C who have not been exposed to prucalopride at any time in their current pregnancy.

In addition, the overall rate/proportion of major structural defects will be compared to the most recently available rate/proportion published from the Metropolitan Atlanta Congenital Defects Program (MACDP) to place the internal comparison group rates in context.

Based on previous OTIS experience, it is expected that the comparison group will be similar to the exposed primary group in terms of key demographics such as maternal age, socioeconomic status, and race/ethnic distribution. However, differences between the cohorts for these demographic factors will be monitored in the annual interim reports and, should they occur, will be addressed in future recruitment efforts and in the statistical analysis phase of the study through methods such as adjustment, detailed in the SAP.

7.4.5 Modalities of Recruitment

Exposed subjects and comparison subjects who are US residents will be recruited through spontaneous contacts with participating OTIS member services in locations throughout the US and Canada. Each OTIS service will provide exposure counseling in the routine manner for all exposed and unexposed women who initially make contact with the service with questions regarding a current pregnancy. Subsequently, each OTIS service will request permission to refer to the Research Center at the UCSD. Potential subjects who agree to be referred will contact the Research Center or be contacted if they prefer. Healthcare providers can also contact the Registry and refer patients; however, in all cases the mother is the individual who provides informed consent for participation and completes the interview-based data collection.

Subjects will also be recruited through other active recruitment strategies, including direct mailings to relevant specialists, obstetric healthcare providers, pharmacists, and exhibits at professional meetings. Clinicians will be made aware of the Registry through the prucalopride prescribing information which contains information about the pregnancy exposure registry (Takeda Pharmaceuticals Company Limited, 2020). This includes the toll-free number for US callers, currently being utilized by all MotherToBaby/OTIS Pregnancy Studies (877-311-8972) and the website address, https://mothertobaby.org/pregnancy-studies/ where clinicians can register subjects. This information is currently listed and will be maintained in the prescribing information for prucalopride. Other methods of increasing awareness will include information about the Registry in product literature and promotional materials, a link on the Takeda website, links to websites for specialty providers and maternal health interest groups, notices posted in

appropriate journals or patient advocacy publications, and presentations at clinical and scientific meetings. The Sponsor may facilitate awareness among prescribers through Medical Science Liaisons. In addition, members of the Scientific Advisory Board for the Registry will be asked to promote recruitment among colleagues.

The existing MotherToBaby/OTIS Pregnancy Studies contact and referral information is available on the study website, and multiple methods are used to increase awareness through the website (https://mothertobaby.org/pregnancy-studies/), social media and print advertising. The FDA website (http://www.fda.gov/womens/registries/default.htm) lists MotherToBaby/OTIS Pregnancy Studies and will have this Registry added to their listing. The study will also be listed on ClinicalTrials.gov.

7.4.5.1 Investigator Selection

This study involves only one site. [redacted], PhD, MPH, who is an epidemiologist and the principal investigator at the [redacted] and has the appropriate experience and access to the research infrastructure, is to conduct this study. The co-investigator is [redacted], MD, who is a pediatrician and expert in birth defects and is the primary major structural birth defects adjudicator.

7.4.5.2 Patient Selection

Pregnant women who are referred to the study by their healthcare provider, by the Sponsor, or who learn about the study through awareness activities and who self-refer, who meet eligibility criteria for the study, and who agree to participate will be selected.

This is an observational study and there are no treatments given or recommended as part of the study procedures. Prescription therapies will be determined solely by the woman's physician.

7.5 Variables

Key exposure, outcome and potential confounding variables are defined below. Additional details regarding definitions are provided in the SAP.

7.5.1 Exposure Variables

Detailed information will be collected on the gestational timing, route of administration, dose, and dates of exposure to prucalopride including the following:

- Maternal exposure to at least one dose of prucalopride from LMP up to and including the end of pregnancy
- Dose of prucalopride
- Duration of prucalopride use during pregnancy
- Indication for use
- Gestational age at time of initial exposure to prucalopride
- Duration (number of weeks) of prucalopride use in pregnancy

Data will be collected through maternal interview(s), medical records, and a pregnancy exposure diary. Maternal interview(s) include questions about pregnancy history, history of onset and other characteristics of CIC or IBS-C, and current medication use. Other variables such as sociodemographic information, gestational age, comorbidities, concomitant medications, disease severity and duration, and other relevant potential confounders will be collected. Information on exposure and CIC and/or IBS-C disease severity-will be collected at enrollment, at 20 weeks to 22 weeks' gestation, and at 32 weeks to 34 weeks' gestation, In addition, exposure data will be collected 0 weeks to 6 weeks after scheduled expected date of delivery or earlier if an outcome has occurred prior to one of the previous interviews. For live births, infant data will be collected at pregnancy outcome and at 12 months of age.

Medical records will be requested from the participant's obstetrician, as well as the healthcare provider treating her CIC or IBS-C. Medical records will also be obtained from the delivery hospital and from the child's pediatrician after birth and at 1 year of age.

Participants will be asked to keep track of their pregnancy exposures and pregnancy-related tests by filling out a pregnancy exposure diary throughout their pregnancy.

7.5.2 Outcome Variables

The outcomes of interest in this study are:

Major structural defects: defined and classified using the US Centers for Disease Control and Prevention (CDC) coding manual that is used for the MACDP classification of major structural defects (CDC, 2017). All major structural defects will be adjudicated by the co-investigator on this study, who is an expert in diagnosing birth defects.

- *Classification of major defects is performed according to the CDC coding list*. The method for classifying major structural defects for purpose of analysis has been described by the study investigators and the OTIS Research Group (CDC, 2017; Chambers et al., 2001) and has been used in previous studies conducted by OTIS. In situations where the CDC coding criteria (CDC, 2017) are unclear for a specific major structural birth defect, the study manager will consult with the Medical Director of the CDCs MACDP.
- *Time period for identification:* major structural defects identified up to 1 year of age by the mother or the healthcare provider/medical record will be included in the primary analysis. Defects identified after that time frame will be described and considered separately.
- *Adjudication of major structural birth defects:* major structural birth defects when reported are first classified by the OTIS study manager once all efforts have been made to obtain adequate information from the mother and infant's healthcare providers. All major structural birth defects are reviewed in detail by [redacted], MD, co-investigator on this study, who is an expert clinical teratologist and dysmorphologist. The co-investigator is always blinded to the pregnancy exposure group at the time of the evaluation.

If additional consultation is required for adjudication or classification, the [redacted] of the CDCs MACDP ([redacted], MD) and members of the Scientific Advisory Board are

available to review cases. The consultants are also blinded to exposure information at the time of the classification review. After this classification has been completed, at each annual interim and final Scientific Advisory Board meeting for the study, the major structural birth defects are reviewed. The members of the Scientific Advisory Board, who are experts in major structural birth defects, as part of the review process, may ask for additional information regarding classification of major structural birth defects, and the investigators may consult with these experts as well. However, at the time of the annual report review, the Scientific Advisory Board members are not blinded to exposure. The final adjudication of the classification of major structural defects is made through this multi-step process and all data presentations derived from the study will clearly describe the adjudication process.

Spontaneous abortion/miscarriage: defined as non-deliberate fetal death that occurs prior to 20.0 weeks post-LMP.

Stillbirth: defined as nondeliberate fetal death anytime in gestation at or after 20.0 weeks post-LMP.

Elective termination/abortion: defined as deliberate discontinuation of pregnancy through medication or surgical procedures. Elective abortions are classified as medical or social.

Premature delivery: defined as live birth prior to 37.0 weeks gestation as counted from LMP (or ultrasound-adjusted date)

Small for gestational age: defined as birth size (weight, length, or head circumference) less than or equal to the 10th centile for sex and gestational age using standard pediatric CDC growth curves for full term or preterm infants (CDC, 2000; Olsen et al., 2010).

Postnatal growth deficiency: defined as postnatal size (weight, length or head circumference) less than or equal to the 10th centile for sex and age using standard pediatric growth curves and adjusted for postnatal age for premature infants if the postnatal measurement is obtained at less than 1 year of age.

Neurodevelopmental milestones in live born children at 1 year of age: Screening for neurodevelopment performed using the Ages and Stages Questionnaire (ASQ). An abnormal score is defined in the scoring guidelines.

Hospitalization in live born children to 1 year of age: defined as any hospitalization of the infant within the first year of life after discharge following delivery.

7.5.3 Potential Confounders

Potential confounders include, but are not limited to:

- Maternal age (years) at due date, continuous and categorical (<25, 25-29, 30-34, >34)
- Paternal age (years) at due date, continuous and categorical (<25, 25-29, 30-34, >34)
- Maternal race (Caucasian/White, Black, Asian, Pacific Islander, Native American, Other)
- Maternal ethnicity (Hispanic, Non-Hispanic)
- Maternal Educational Category (years of completed education <12, 12-15, >15)
- Hollingshead Socioeconomic Category based on maternal and paternal occupation and education (1-5)
- Maternal height (cm)

- Maternal prepregnancy body weight (kg)
- Maternal prepregnancy body mass index (BMI) (<18.5, 18.5-24.9, 25-29.9, ≥30)
- Number of times ever pregnant (1, 2-3, 4-5, ≥6)
- Number of previous live birth deliveries (0, 1-2, 3-4, ≥5)
- Number of previous stillbirth outcomes (0, 1 2, 3 4, ≥5)
- Number of previous pregnancies ending in spontaneous abortion/miscarriage (0, 1, 2, ≥3)
- Number of previous pregnancies ending in elective termination/abortion (0, 1, 2, ≥3)
- Number of previous pregnancies resulting in a malformed fetus/infant
- Gestational age (weeks) of pregnancy at time of enrollment, continuous and categorical (<13, 13-19.9, ≥20): gestational age is calculated from the first date of LMP
- Referral source (Sponsor, OTIS service, HCP, Internet, Other)
- A measure of disease severity (PAC-SYM) and collected at each interview during pregnancy
- Prenatal, multivitamin or folic acid supplement use by timing (began prior to conception, post-conception only, not taken at all)
- Alcohol use in pregnancy (yes/no)
- Tobacco use in pregnancy (yes/no)
- Prenatal diagnostic tests performed prior to enrollment (Ultrasound level 1, Ultrasound level 2, Chorionic Villus Sampling, Amniocentesis)
- Prenatal diagnostic tests performed anytime in pregnancy (Ultrasound level 1, Ultrasound level 2, Chorionic Villus Sampling, Amniocentesis)
- Maternal pregnancy exposure to another known human teratogen (eg, isotretinoin)
- Years since diagnosis of CIC or IBS-C
- Comorbid maternal medical history (diabetes, infertility, chronic hypertension)
- Exposure to other medications and vaccines during pregnancy
- Exposure to infections during pregnancy

7.6 Data Sources

Data will be collected using maternal interview(s), the ASQ, medical record reviews, and a pregnancy exposure diary. Data will be recorded on hard copies of forms and these records will be retained by OTIS. These forms are considered the primary data sources for the study. Data from these forms will be extracted and entered into a customized OTIS study database located in the Research Center and developed specifically for the OTIS studies. In addition, a data tool for assessing disease severity/activity will be selected.

7.7 Study Size

Recruitment goals are set at 103 subjects per year in the prucalopride-exposed group, and 103 subjects per year in the disease comparison group, as shown in Table 1, for a total of 616 subjects over a 3-year recruitment period. As the study progresses, subjects recruited to the disease-matched comparison group will be recruited using frequency matching by CIC or IBS-C to the prucalopride-exposed group. However, it is not feasible to match on a 1-to-1 basis as this could lead to declining to enroll eligible disease-matched comparison subjects if they happen to come into contact with the registry before a prucalopride-exposed pregnancy. Therefore, balance

in the cohort numbers will be monitored on a monthly basis, and overall balance addressed by adjusting recruitment activities as needed. It is not possible to predict the number of pregnancy exposures that will occur for a newly marketed medication, or whether the recruitment rates will be equal in all years; therefore, the sample size is based on estimates that may require revision as the study progresses.

Table 1 Anticipated Recruitment Timetable and Sample Size

Year 1	Year 2	Year 3
Enroll	**Enroll**	**Enroll**
103 exposed	103 exposed	103 exposed
103 comparison	103 comparison	103 comparison

7.7.1 Determination of Sample Size

Based on previous experience with OTIS studies, the investigators estimate that subjects will be an average of 7 weeks to 10 weeks post-LMP at the time of enrollment. Given this mean gestational timing at enrollment, the anticipated spontaneous abortion/miscarriage and stillbirth rate is 10%, the estimated elective termination/abortion rate is 10%, and the estimated lost to follow-up rate is 5% (based on previous OTIS experience), which would result in known outcomes for approximately 292 pregnancies in each group, of which 231 in each group will result in at least one live born infant.

Baseline rates of major structural birth defects, spontaneous abortion, premature delivery, and small for gestational age are based on previous MotherToBaby/ OTIS studies and on general population data. Table 2 gives the minimum detectable relative risks with 80% power (2-sided significance level 0.05), for the comparison described above.

Table 2 Sample Size and Power for a Specified Effect Size

Outcome	N in Exposed Group	Rate in Comparison Group	Relative Risk	Power[a]
Major structural defects[b]	231	3%[c]	3.0	80%
Spontaneous abortion/still birth	261	10%[d]	1.8	80%
Preterm delivery	231	10%[e]	1.9	80%
Small for gestational age	231	10%[f]	1.9	80%

[a] Arcsine transformation using pwr.2p.test() in R package 'pwr' to obtain effect size h, where $h = 2 * \sin^{-1}\sqrt{p_1} - 2 * \sin^{-1}\sqrt{p_2}$ and p_1 = event rate in the exposed group, p_2 = event rate in the comparison group, assuming 2 sided alpha = 0.05.
[b] Primary endpoint; among livebirths.
[c] CDC, 2017.
[d] Ammon Avalos et al., 2012.
[e] Ferré et al., 2016. MMWR Morb Mortal Wkly Rep 2016;65:1181–1184. DOI: https://www.cdc.gov/mmwr/volumes/65/wr/mm6543a1.htm
[f] CDC, 2017; Nellhaus, 1968; Olsen et al., 2010.

7.8 Data Management

Data will be collected using maternal interview(s), ASQ, medical record reviews, and a pregnancy exposure diary. Data will be recorded on hard copies of forms and these records will be retained by OTIS. These forms are considered the primary data sources for the study. Data from these forms will be extracted and entered into a customized OTIS study database located in the Research Center and developed specifically for the OTIS studies.

The database itself has built in range limits for key variables that prevent certain data entry errors. In addition, all data entry forms will be reviewed for logical errors by the study data manager on a regular basis and 100% of key variables will be double-checked for data entry accuracy. The study statistician will also conduct reviews of the cumulative data from the study in the database for distributions and values that are illogical. The study manager will be responsible for working with the data manager and the supervisory staff to oversee the data validation procedures.

Access to the database will be controlled by password, with different access privileges assigned to the data entry staff and administrative staff; these privileges are outlined in detail in the OTIS Data Management Guide, Data Entry standard operating procedures (SOP), and supplements to these guides. An audit log is built into the database to archive all such entry edits.

Hard copies of patient files and subject signed consent forms will be kept in a locked cabinet under the supervision of the study investigators. Data collection and validation procedures will be detailed in appropriate operational documents.

7.8.1 Data Quality Control

The data will be entered by trained study personnel with experience with this type of information. Data will be collected and entered into the database according to the SOP for data collection and data entry established for this study.

The data manager will calculate monthly error rates for each data entry staff person and for the study overall, and will recommend and initiate training/retraining where quality standards are not being met. The study manager will oversee this process and verify that training standards are achieved.

For the primary study outcome, verification of the outcomes identified and classification will be provided by blinded review by co-investigator, [redacted], MD.

7.8.2 Data Collection Schedule

Data will be collected according to the schedule described in Table 3. After oral informed consent, a maternal telephone interview(s) will be conducted. Depending on the gestational age at enrollment, up to two additional telephone interviews will be scheduled in the second and third trimesters of pregnancy. Written informed consent will be requested following the intake interview. In addition:

An outcome telephone interview will be planned for 0 weeks to 6 weeks after delivery.

After the end of pregnancy, medical records release forms for the obstetric provider, delivery hospital, pediatrician, and any specialty care provider for the indicated disease, will be sent to the mother for signature. Once the record release forms are received, records will be requested from the providers and, upon their receipt, data will be abstracted.

The ASQ will be sent to the mother to complete when her child is approximately 1 year.

A 1-year pediatric evaluation release form will be sent to the mother and, once signed, will be used to request data from the pediatric care provider.

7.8.3 Data Collected

Data on the numbers of potential subjects referred into the study, eligible for enrollment, consented, unable to contact, or declined participation will be collected and summarized monthly at the Registry Research Center.

7.8.4 Disposition of Patients

Women who are not eligible for enrollment in the study or who decline will be tallied in monthly recruitment reports, but these data will not be included in the annual interim or final study reports.

Table 3 Timing of Cohort Enrollment, Interviews, Examinations, and Medical Records

	Anytime in Pregnancy	20-22 Weeks Gestation[b]	32-34 Weeks Gestation[c]	0-6 Weeks After Delivery	0-12 Months After Delivery	1 Year After Delivery
Referral[a]	√					
Enrollment and Consent[a]	√					
Intake/Enrollment Interview[a]	√					
Interim Interview I		√				
Interim Interview II			√			
Pregnancy Outcome Interview and Request for Medical Records				√		
Medical Record Review					√	
Developmental Screening / ASQ						√
Pediatric 1-Year Medical Records Request and Review						√

[a] Subjects can enroll into the study at any time during pregnancy.
[b] If subject is enrolled and Intake Interview is conducted after 18 weeks' gestation, only one interim interview will be conducted during pregnancy at 32-34 weeks gestation.
[c] If subject is enrolled and Intake Interview is conducted at 30 weeks' gestation or after, no Interim Interview will be conducted.

7.8.5 Patient Data

The OTIS Research Center is responsible for verifying the subject selection criteria, enrolling each subject and securing informed consent, oral and written (when available or applicable), providing all pregnancy (intake/enrollment and interim) and post-partum follow-up interviews and medical record review, recording and storage of all data, and subsequent data analysis and interpretation.

7.8.5.1 Intake/Enrollment Interview

Following verbal informed consent, a structured maternal intake telephone interview will be conducted by a trained Research Associate at the OTIS Research Center. This interview will include questions on the following: pregnancy history; current health history; prepregnancy weight and height; socioeconomic and demographic information including maternal and paternal occupation, education and ethnicity, and income category; current medication use, both prescriptive and over the counter; other environmental or occupational exposures, alcohol, tobacco, caffeine and illicit drug use; current pregnancy complications including illnesses; and history of onset and other characteristics of the disease the participant is enrolled for, if applicable. Women will be asked to respond to a measure of disease severity, the PAC-SYM for CIC or IBS-C to provide a means of assessing potential confounding or effect modification by disease severity in the final analysis.

Following the initial intake interview, participants will be sent a pregnancy exposure diary on which they will be asked to record any additional exposures (medications, vaccinations, vitamins, etc.) or events as the pregnancy progresses. Along with the pregnancy exposure diary, each woman will be sent two copies of the informed consent document, one for her own records, and one to sign and mail back to the study.

7.8.5.2 Interim Interviews I and II (20 and 32 Weeks' Gestation)

Women who have enrolled in the study prior to 18 weeks post-LMP will be interviewed by telephone at 20 weeks to 22 weeks post-LMP, 32 weeks to 34 weeks post-LMP and within 0 weeks to 6 weeks after the expected due date.

Women who have enrolled after 18 weeks post-LMP will be interviewed at 32 weeks to 34 weeks post-LMP and within 0 weeks to 6 weeks after the expected due date.

Women who have enrolled after 30 weeks post-LMP will be interviewed within 0-6 weeks after the expected due date (Table 3).

The purpose of these interviews will be to update records of pregnancy exposures and results of prenatal tests, to remind women to maintain the pregnancy exposure diary, to update phone number and address information, and to determine if the pregnancy has ended prior to the expected due date.

7.8.5.3 Pregnancy Outcome Interview

At any of the interim interview points, if the pregnancy has ended, the outcome interview will be conducted at this time or at the earliest convenient time for the mother. For women who are still

pregnant at the 32 weeks to 34 weeks interview, the outcome interview will be conducted within 0 weeks to 6 weeks after the expected due date.

The outcome interview for live born infants will be a structured telephone interview and information will be elicited on the following: date of delivery, hospital location and mode of delivery; sex, birth weight, length and head circumference; Apgar scores; description of delivery or birth complications including major structural defects; type and length of hospital stay for mother and infant; delivering physician's and infant physician's names and addresses; method of infant feeding; pregnancy weight gain; and additional exposures and results of prenatal tests occurring since the previous interview.

The outcome interview for spontaneous abortion/miscarriage or elective termination/abortions will also be structured and information will be elicited on the following: date and type of outcome; hospital location if applicable; prenatal diagnosis; pathology results if available; and additional exposures and results of prenatal tests occurring since the previous interview(s). The outcome interview for stillborn infants will include all of the above, plus information on sex, birth size and autopsy results if available.

Major structural defects, spontaneous abortions/miscarriage, elective terminations/abortion, fetal or neonatal/infant deaths occurring in the prucalopride-exposed group will be reported to the sponsor within 24 hours of the Research Center staff learning of the event. These reports will be made using the FDA's MedWatch form. The sponsor will be responsible for directly reporting to the FDA for events involving their product according to regulatory guidelines (Section 11).

7.8.5.4 Medical Records and General Pediatric Evaluation

Upon completion of the outcome interview, each woman will be mailed a packet containing medical records release forms for the delivery hospital, obstetrician, pediatrician, and specialty physician. For women whose pregnancies have ended in spontaneous abortion/miscarriage or elective termination/abortion or stillbirth, records release forms will be mailed for prenatal diagnosis, and pathology or autopsy reports if available. Each woman will be asked to sign the medical records release forms, as well as a Health Insurance Portability and Accountability Act (HIPAA) Authorization Addendum (if applicable), and to return these authorization documents along with the pregnancy exposure diary form.

Upon receipt of the signed medical records release forms, a standard physical evaluation form will be mailed to each pediatrician or other physician responsible for the care of each live born infant. This form includes information on infant size at the time of the latest examination and an open-ended question about postnatal complications and congenital anomalies.

At 1 year of age, another medical records release form for the pediatrician or healthcare provider caring for the child will be sent to the mother for signature, and the signed form with a standard physical evaluation form will be sent to the healthcare provider to request updated information on growth, and congenital defects.

7.8.5.5 Ages and Stages Questionnaire

When the child is 1 year of age, the mother will be asked to complete the Ages and Stages (ASQ) developmental screening questionnaire (Squires et al., 2009).

7.8.6 Procedure and Consequences for Subject Withdrawal From Study Schedule

As stated in the informed consent, any study participant may withdraw from the study at any time for any reason; however, data that have been collected up to the time of withdrawal may be used by the researchers. Women who withdraw from the study after the collection of birth outcome will not be considered lost to follow-up. Women who withdraw from the study prior to the collection of birth outcome will be considered lost to follow-up and the SAP addresses the method whereby these data will be reported.

7.9 Data Analysis

7.9.1 Analysis Software

All summaries and statistical analyses will be performed using the current version of open source statistical programming language R and StatXact.

7.9.2 Analysis Variables

7.9.2.1 Outcome Classification for the Primary Outcome - Major Structural Defects

The method for classifying major structural defects for purpose of analysis has been described by the study investigators and the OTIS Research Group (CDC, 2000; Olsen et al., 2010) and has been used in previous studies conducted by OTIS.

7.9.2.2 Inclusion Criteria for the Primary Outcome – Major Structural Defects

Definition: A major structural defect is defined as a defect that has either cosmetic or functional significance to the child (eg, a cleft lip).

Classification of major defects will be performed according to the CDC coding list (CDC, 2017) and applied equally across all cohorts in the study. Some major structural defects are known consequences of pregnancy events, such as premature delivery, and are therefore not directly due to drug exposure. For example, isolated patent ductus arteriosus or isolated inguinal hernia in an infant delivered before 36 weeks' gestation are considered consequences of prematurity, and therefore, using CDC coding criteria, none of these defects are counted as major structural defects. Other structural defects, such as club foot or cranial synostosis, could be due to position of the infant in the uterus or could be primary defects initiated earlier in pregnancy. In most cases, it is not possible to know the true onset or etiology of the defect. Therefore, using CDC coding criteria, these anomalies are counted as major structural defects uniformly across all cohorts.

Using CDC coding criteria, chromosomal anomalies are counted as major structural birth defects. Although it is unlikely that a drug exposure could cause a chromosomal defect, it is not impossible. These major structural defects are counted uniformly across all cohorts in the study.

This uniform coding reduces differences in outcome definitions between studies for a better interpretation of results in the event they are compared. Further, it allows for the use of the external comparator group compiled by the MACDP. It is anticipated that the occurrence of defects that are unrelated to drug exposure in the proposed study population will be nondifferential across cohorts. Therefore, their inclusion, when indicated, represents part of the baseline risk for major structural defects in each cohort. This should not impact the risk estimates and measures of association.

With respect to known chromosomal or genetic defects, a sensitivity analysis is planned, and outlined in the SAP, that will exclude these defects.

Time period for identification: major structural defects identified up to 1 year of age by the mother or the healthcare provider/medical record will be included in the primary analysis. Defects identified after that time frame will be described and considered separately.

Confirmation of defects: independent confirmation of certain defects will be required. For example, a heart murmur thought to represent a ventricular septal defect prior to 1 year of age will be included if it is confirmed as a heart defect by cardiac ultrasound. Similarly, a midline cutaneous marker at L2-L3 noted will be included as occult spinal dysraphism only if confirmed by appropriate imaging studies.

7.9.2.3 Exclusion Criteria for the Primary Outcome – Major Structural Defects

Defects will be excluded based on criteria outlined in the CDC coding list and Section 7.9.2.2.

Time period for identification: structural defects ascertained after 12 months of age will not be included in the primary analysis, but will be considered separately in the context of a possible pattern.

Defects identified in spontaneous abortions/miscarriage or elective terminations/abortions: defects identified by prenatal ultrasound or examination of the products of conception following elective or spontaneous abortion/miscarriage will not be included in the primary analysis due to potential bias involved in non-uniform use of prenatal diagnosis and pathology evaluation for all abortuses; however, these defects will be considered in a secondary analysis including all defects in the numerator over all pregnancies with known outcome in the denominator (excluding lost to follow-up).

Major structural defects identified in an ongoing pregnancy: Major structural defects identified by prenatal ultrasound prior to enrollment in an ongoing pregnancy will disqualify the pregnant woman from enrolling in the prospective cohort. She will be invited to join “Exposure Case Series”, as described in Section 7.4.3.

7.9.2.4 Outcome Classification for Secondary Outcomes

Spontaneous abortion/miscarriage: spontaneous abortion/miscarriage is defined as non-deliberate fetal death which occurs prior to less than 20.0 weeks post-LMP.

Stillbirth: stillbirth is defined as non-deliberate fetal death anytime in gestation at or after 20 weeks post-LMP.

Elective termination/abortion: elective termination/abortion is defined as deliberate termination of pregnancy at any time in gestation. Reasons for elective abortions are captured and are classified as due to medical reasons or social reasons.

Premature delivery: premature delivery is defined as live birth prior to 37.0 weeks gestation as counted from LMP (or calculated from first-trimester ultrasound-derived due date if last menstrual period uncertain or more than 1 week discrepant). Elective caesarian deliveries or inductions prior to 37.0 completed weeks will be considered separately.

Small for gestational age: small for gestational age is defined as birth size (weight, length or head circumference) less than or equal to the 10th centile for sex and gestational age using standard pediatric CDC growth curves for full term or preterm infants (CDC, 2000; Olsen et al., 2010).

Postnatal growth deficiency: postnatal growth deficiency is defined as postnatal size (weight, length or head circumference) less than or equal to the 10th centile for sex and age using National Center for Health Statistics (NCHS) pediatric growth curves, and adjusted postnatal age for premature infants if the postnatal measurement is obtained at less than 1 year of age (CDC, 2000).

Hospitalizations: hospitalizations are defined as infants admitted to the hospital in the first year of life for any indication.

Achievement of Developmental Milestones: one or more domains scored as abnormal on the ASQ completed by the mother when the infant is approximately one year of age will define achievement of developmental milestones.

7.9.3 Statistical Methods

All aspects of the final analysis summarized below are further detailed in the SAP.

Demographic and baseline characteristics will be summarized within each cohort and compared between groups.

7.10 Analyses of Primary Outcome

For the primary endpoint of major structural defects, the exposure of interest is prucalopride exposure at any time from the DOC to the end of the first trimester. The primary comparison will be the birth prevalence of major structural defects between exposed group and unexposed group among pregnancies resulting in at least one live born infant. A point estimate of the crude (ie, unadjusted) risk ratio (RR) of the exposed group versus the unexposed group, as well as its 95% confidence interval (CI) will be computed using normal approximation method. When the expected frequency of any of the cells of the contingency table is less than five, the CI will be obtained by an exact method using the software StatXact. The comparison will also be carried out within each of two strata, according to whether the woman had prenatal diagnostic testing,

such as level 2 ultrasound, amniocentesis or chorionic villus sampling, prior to enrollment in the study or not.

Due to the observational nature of the study, the above crude estimate of RR will be further adjusted for potential confounders (Rosenbaum, 2002), provided that there are sufficient number of events. A list of potential confounders will be provided in a separate table for each outcome prior to the final analysis, based on scientific knowledge including literature review. In addition, all of the following three criteria will be applied in accordance with the definition of confounders (Greenland et al., 1999; Xu et al., 2018): 1) by assessing each considered variable in a logistic regression model containing the exposure variable and the outcome variable to determine if inclusion of that single covariate changes the estimate of the odds ratio for exposure by 10% or more; 2) standardized mean differences greater than 0.1; 3) association with the outcome with p-value <0.2 in the unexposed cohort. Care will be taken not to include those variables that are strongly associated with the exposure variable but only weakly associated with the outcome variable.

The confounders identified above will be used to build the propensity score for exposure (Rosenbaum, 2002). R package 'twang' or similar R package available at the time of analysis will be used for this purpose, following which standardized mean differences will be used to check the balance of the covariates between the cohorts.

The primary analysis will be performed with inverse probability weighting (IPW) using the propensity score. In the IPW approach, we will use stabilized weights that are further trimmed to be between 0.1 and 10 if necessary (Austin and Stuart, 2015). The robust sandwich variance estimator will be used following the IPW approach.

A secondary analysis will be conducted using outcome regression ie, a logistic regression model will be fitted with major structural defect (Y) as outcome, and exposure (A) and propensity score (L) as regressors. Standardization will be performed to obtain the estimated causal risk ratio (Hernán and Robins, 2019). The CI's are obtained by 10,000 bootstrap, ie, resampling with replacement of the pregnant women.

Sensitivity analyses will be performed for the primary outcome:

- The first sensitivity analysis will be performed for the outcome of major structural birth defects among all pregnancies excluding those that are lost-to-follow-up. The analysis population will be Cohort 1 with exposure to the drug at any time from DOC to the end of the first trimester including all pregnancies with known outcome (ie, excluding those that are lost-to-follow-up). The analysis population for Cohort 2 will be all pregnancies excluding those that are lost-to-follow-up.
- The second sensitivity analysis will be performed for the outcome of major structural birth defects excluding those defects thought to be of chromosomal or genetic origin.
- The third sensitivity analysis will be performed for the outcome of major structural birth defects stratified on any abnormal finding (yes/no) among those with prenatal testing prior to enrollment.

- Sub-analyses using graphical presentation based on gestational timing as well as dose of exposure to Prucalopride will also be performed.
- Exposure to a known human teratogen is already included in the list of potential confounders for Cohort 1 vs. Cohort 2. However, in the case where there are insufficient number of events to consider regression adjustment, a sensitivity analysis will be performed to exclude subjects with exposure to known teratogens in Cohort 1 and Cohort 2 to address this potential confounder.

7.11 Analyses of Secondary Outcomes

1) Pregnancy Outcomes

The analysis of SAB and stillbirth is complicated by left truncation in the data, ie, women enter the study at arbitrary times in gestation. Only those women who are enrolled prior to 20.0 weeks of gestation are eligible for the analysis of SAB. Since they are not followed from gestational age zero, survival analysis methods will be used to handle left truncation, as well as right-censoring when a subject is lost-to-follow-up prior to 20.0 weeks' gestation. Left-truncated Kaplan-Meier estimates at 20 weeks' gestation will be used to estimate the SAB rate in each of the cohorts (Tsai et al., 1987). The Cox proportional hazards regression models incorporating left truncation will be used to estimate the hazard ratio (HR) of different cohorts, as well as to obtain the 95% CIs. Stillbirth will be analyzed in a similar fashion.

The analysis of elective termination/abortion will be descriptive.

To account for potential confounding, propensity score methods described above will be applied. In particular, IPW approach will be used with the Cox model to obtain the adjusted HR.

The analysis of premature delivery can also be complicated by left truncation in the data, ie, women enter the study at arbitrary times in gestation. Only those women who are enrolled prior to 37.0 weeks of gestation are eligible for the analysis of premature delivery. These data will be analyzed similarly to SAB, as described above, using survival analysis methods, to handle possible left truncation and right-censoring.

2) Infant Outcomes

The following are binary endpoints: small for gestational age (SGA) at birth in weight, height and head circumference, respectively, growth deficiency at about one year of age in weight, height and head circumference respectively. The analysis of each of these outcomes will be similar to the analysis of the primary outcome, based on all pregnancies resulting in live born singletons.

Multiple births will be included in the analyses of hospitalization in the first year of life and any one or more domains scoring abnormal on the ASQ-3 at about one year of age. The outcome variables will thus likely contain correlated data such as twins, and the generalized estimating equations (GEE) approach will be used (Liang and Zeger, 1986; Diggle, 2002). The causal effect

will be estimated similar to the primary outcome, but in place of logistic regression it will be GEE with the logistic link function. The CI's are obtained by 10,000 bootstrap.

7.12 Missing Data

Multiple imputation (MI) will be conducted to handle the missing data. Further details are provided in the SAP.

7.12.1 External Comparisons

The overall rate/proportion of major structural defects will be compared with the most recently available rate/proportion published from the MACDP to place the internal comparison group rates in context. However, it should be noted that the MACDP rates for major birth defects represent a population from one urban city that differs in many respects from the sample of women with the indications that are eligible for this study.

7.12.2 Evaluation for a Pattern of Major Structural Defects

The following steps will be taken to evaluate any pattern of major structural defects:

A review of major structural defects will be made by category. A review of specific major structural defects will be conducted taking into consideration timing, dose, and biological plausibility.

Major structural defects identified in aborted fetuses will be reviewed separately from the primary analysis for the live born infants.

7.12.3 Lost to Follow-Up

Pregnancies enrolled in the cohort study for which outcome information is unobtainable within 1 year after the estimated date of delivery are considered lost to follow-up. It is possible that outcomes among pregnancies lost to-follow-up could differ from those with documented outcomes. Because of differences in follow-up and reporting patterns, it is currently not possible to assess with any certainty what impact with regard to potential biases the lost to follow-up may have on any analysis of the cohort study. Should lost to follow-up numbers be substantial, however, efforts at comparing some of the characteristics of each group will be made in an attempt to address this potential source of bias. However, the OTIS Research Center prior experience has been that the lost to follow-up rate is extremely low, typically 5%.

7.12.4 Interim Analysis and Termination of the Study

The Registry will develop an annual interim report and any additional ad hoc reports with the advice of the Scientific Advisory Board members. Each report will be a composite of the cumulative data to date and will supersede any previous reports. Descriptive analyses may be presented, but no formal interim statistical analysis is planned. The final analysis will be conducted when the cohort study has been completed. The study may be terminated at any time based on a variety of considerations. This decision will be considered and a recommendation made upon review by the Scientific Advisory Board (Section 10.7.1).

Each interim and the final report for the Registry will provide a summary of the literature regarding prucalopride exposure and pregnancy outcomes at the time of the submission of each study report.

7.13 Quality Control

Interviews will be recorded on hard copies, and medical record abstraction will be recorded electronic forms and these records will be retained at the Research Center. Data from these forms will be extracted and entered into a customized database located at the Research Center. The data will be extracted and entered by trained study personnel with experience with this type of information. Entries will be periodically reviewed for logical errors, and a random subset of intake and outcome forms will be double-checked for data entry accuracy. The method and duration of storage of data is addressed in the informed consent. Access to the database will be controlled by password. Hard copies of patient files and subject signed consent forms will be kept in a locked cabinet under the supervision of the study investigators.

7.14 Limitations of the Research Methods

The primary limitation of a cohort study utilizing volunteer subjects is potential selection bias. The use of comparably selected unexposed pregnancies will address this concern to some extent. However, women who agree to enroll in the cohort study may represent particularly high or low risk pregnancies (Johnson et al., 2001). The study results will be strictly generalizable to women fitting the profile of the sample of women who enroll.

Another limitation of the study design relates to the evaluation of spontaneous abortion/miscarriage rates. Rates of early spontaneous abortion/miscarriage, ie, at 7 weeks to 9 weeks post-LMP or less, will not be measured in a study that enrolls women after recognition of pregnancy. The study results with respect to spontaneous abortion/miscarriage will be limited to relative risk for late first-trimester and early second-trimester pregnancy loss. The subset of participants who are eligible for this analysis is restricted to those who enroll prior to 20.0 weeks' gestation. Although it has not been the OTIS experience in previous studies, if a high proportion of women enroll in the study after 20.0 weeks' gestation, the statistical power for detecting risks of spontaneous abortion/miscarriage will be reduced. In addition, if a high proportion of women enroll later in pregnancy, other survival biases may be introduced. A sensitivity analysis by gestational age at enrollment will be performed in order to address these questions.

Because early prenatal testing is so prevalent in the US, it may be difficult to achieve adequate numbers of patients if all pregnancies with prior prenatal testing are excluded from the analysis. Therefore, the Registry will include pregnancies enrolled prior to outcome but after a prenatal test has been performed as long as the test does not indicate the presence of a major structural defect. The FDA guidance document (Postapproval Pregnancy Safety Studies: Draft Guidance for Industry (FDA, 2019) acknowledges that such an approach may be necessary to accrue adequate numbers. However, this practice could potentially bias the results by lowering the overall estimate of the prevalence of birth defects (Honein et al., 1999). The data analysis will address this in each interim and the final study report by sub-analysis stratifying on use of prenatal diagnostic testing.

The calculation of frequency of birth defects excludes fetal losses (spontaneous abortions, induced abortions, or fetal deaths) for which no birth defects have been detected as they may introduce a classification bias. It is unknown what percentage of these pregnancies consists of potentially normal outcomes or birth defects. The Registry attempts to obtain information on birth defects detected at the time of the outcome. However, the malformation status of the aborted fetus may not be known. For this reason, the primary comparison for this outcome of the study will be conducted among pregnancies ending in live birth, and a secondary analysis of this outcome will include all pregnancies with known outcome.

It is expected that exposures to prucalopride will occur in unintended pregnancies. Although more than half of all pregnancies in the US are unintended (Henshaw, 1998), the possibility of confounding by age, race, and other demographic variables will be considered. For example, the rate of unintended pregnancies is higher among low-income women/families than among other socioeconomic groups. It is possible that demographic variables will be associated with treatment as well. As such, these factors will be taken into consideration in the recruitment of comparison groups and in the analysis.

It is not possible to predict the number of pregnancy exposures that will occur for a newly marketed medication, and therefore, sample size is based on estimates that may require revision as the study progresses.

The study design has relative strengths with respect to the control of a large number of potential confounders. Information will be collected repeatedly throughout pregnancy on a variety of factors that may be related to exposure and to pregnancy outcome, and the use of a disease-matched comparison group addresses to some extent the issue of confounding by indication. Misclassification bias due to poor recall is thought to be reduced in prospective study designs such as this one. In addition, each subject is interviewed at several predetermined intervals during pregnancy. Misclassification bias in the outcome is minimized in this study design through the use of a standardized evaluation protocol. Another strength of the study design is the anticipated minimal lost to follow-up rate. Based on previous experience of the investigators in the OTIS/MotherToBaby Pregnancy Studies, and the frequent subject contact, lost to follow-up is expected to be 5%, and therefore not expected to pose a threat to the validity of study results.

Finally, the small sample size that is projected to be achievable for this Registry has limitations in statistical power. However, the projected sample size is sufficient to detect a 3-fold relative risk for major structural defects overall in exposed pregnancies compared to unexposed, is similar in size to other pregnancy registries, and is an important method for early evaluation of a newly marketed medication for safety in pregnancy. The investigators and the Advisory Board's expert review and comment on the data and the inclusion of evaluation of a pattern of major anomalies are strengths.

7.15 Registry Case Report Management

The focus of the Registry will be the hypothesis-driven cohort study; however, the Registry will also function as a repository for case reports, ie, the Exposure Case Series described in

Section 7.4.3 of pregnancies that do not qualify for the cohort study. The management of the exposure case series and how they will be described is outlined.

7.15.1 Source of Participants

Pregnant women who qualify for the prospective cohort study may be self-referred to the Registry, come through healthcare providers, or come from the Sponsor's Safety group. Pregnant women who do not qualify for the prospective cohort study may be self-referred to the Registry.

7.15.2 Healthcare Provider Initiated Reports

If the Registry is initially contacted by the healthcare provider, he or she will be asked to have the pregnant patient contact the Registry to provide informed consent and if the patient qualifies for the cohort study, she will be followed in that manner. If she does not qualify for the cohort study, but has had exposure to prucalopride in pregnancy, she will be asked to enroll in the Registry Exposure Case Series.

7.15.3 Sponsor Safety Surveillance of Pharmacovigilance

The Sponsor will provide the Registry with the number of reports of pregnancy exposures to prucalopride received through the safety surveillance processes or other sponsored studies in order to assist with evaluating potential for recruitment, and will encourage reporters to contact the Registry directly, or transfer callers directly to the Registry.

7.15.4 Reports from Published Literature

Relevant reports from the published literature will be included in the Registry Annual Interim and Final Reports as appendices and will be reviewed and discussed at the annual Scientific Advisory Board meetings.

7.15.5 Information from Other Studies

As other data sources on pregnancy outcomes following maternal exposure to prucalopride during pregnancy become available, they may be summarized and reported in the Registry Annual Interim and Final Reports.

8. PROTECTION OF HUMAN SUBJECTS

8.1 Responsibilities of the Investigator and the OTIS Research center

The Investigator will perform the study in accordance with this protocol, applicable local regulations and international guidelines.

The OTIS Research Center is responsible for taking all reasonable steps and providing adequate resources to ensure the proper conduct of the study.

The OTIS Research Center is responsible for:

- Local submission(s) complying with data protection rules
- Any other local submission(s)

8.1.1 Participant Information and Consent

The Registry will ensure protection of participant personal data and will not include participant names on any reports, publications, or in any other disclosures, except where required by law. The informed consent form will be in compliance with UCSD regulatory requirements. The informed consent forms used in this study, and any changes made during the course of the study, must be prospectively approved by the UCSD Institutional Review Board (IRB) before use.

The Registry staff ensures that each study participant, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The Registry will obtain informed consent from each participant or participant's legally acceptable representative before any study-specific activity is performed. The pregnant woman must agree to the oral consent form at the time of enrollment and before completing the intake interview. The UCSD IRB has granted the study a waiver of written consent to enroll and participate in the phone interviews due to minimal risk. She must also sign for release of medical information and the HIPAA authorization (if applicable) to allow the Registry to obtain information on the pregnancy and the pregnancy outcome from the participant's obstetric healthcare provider, the hospital of delivery, and any healthcare specialist for treatment of the indicated disease, and for the infant from the infant's pediatric healthcare provider. The original oral and signed written informed consent documents and HIPAA authorizations will be maintained by the Registry Office. The original medical record release documents will be retained at the Registry office as well, and copies will be sent to the institution or physician from whom records are being requested. These medical release documents are in the authorized format required by the UCSD and are compliant with HIPAA regulations.

8.1.2 Participant Withdrawal

Participants may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or administrative reasons. In any circumstance, every effort will be made to document subject outcome, if possible. The Registry routinely inquires and records the reason for withdrawal. If the subject withdraws from the study, no further data will be collected, but the Registry will retain and continue to use any data collected prior to the withdrawal of consent.

8.1.3 Institutional Review Board

According to the FDA guidance document, registries such as this must comply with ethical principles and regulatory requirements involving human subjects research. Therefore, the study protocol and informed consent documents must be approved by the IRB at UCSD. The chairman or the recording secretary of the IRB must have signed a form indicating approval. Notification of the Board's approval of the study must be provided to the Sponsor prior to initiation of participation in the Registry.

The Registry follows the FDA Guidance for Industry for regulatory reporting of serious adverse events (SAEs) to the FDA. "The Agency considers pregnancy exposure registry reports (both prospective and retrospective) as derived from active solicitation of patient information. Accordingly, a sponsor holding marketing authorization for an approved drug or licensed biological product must submit to the Agency, within 15 calendar days, reports of adverse events from the registry that are both serious and unexpected by regulatory definition and where a reasonable possibility exists that the drug or biological product caused the adverse event" (National Institutes of Health, 2003).

For FDA status reporting the Registry interim report can be appended to the submission as described in the FDA guidance (National Institutes of Health, 2002). The Annual Report contains the background, study design, and summary of the analysis plan. It summarizes the study status and the cumulative data on the Registry to date. In addition, the Registry annual report contains individual line listings for specific outcomes, such as major structural defects, to assist the Sponsors in preparation of their submission. The Registry reports will be current to the most recent data cutoff period.

9. ETHICAL AND REGULATORY STANDARDS

9.1 Ethical Principles

This study will be conducted in accordance with the ethical principles of the Declaration of Helsinki (1995), and the HIPAA (National Institutes of Health, 2002; Andrews et al., 1996).

9.2 Laws and Regulations

This Registry will be conducted in compliance with the protocol, International Society for Pharmacoepidemiology's Guidelines for Good Epidemiology Practices for Drug, Device, and Vaccine Research in the US, US FDA regulatory requirements, in accordance with the ethical principles of the Declaration of Helsinki (1995).

10. ADMINISTRATIVE CONSIDERATIONS

10.1 Data Protection

The individual participant personal data is incorporated into the study records and the study database, and will be treated in compliance with all local applicable laws and regulations. The Registry makes every effort to assure patient confidentiality within the Registry. When information is distributed to Scientific Advisory Board members, no contact information or direct patient identifiers are included. No patients are identified in study presentations or publications.

When archiving or processing personal data pertaining to study participants, the OTIS Research Center will take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

10.2 Insurance

The University of California provides insurance for researchers and research activities conducted by academic Investigators including this study.

10.3 Disclosure of Data

10.3.1 Confidentiality

The Registry makes every effort to assure patient confidentiality within the Registry. When information on reports is distributed to Scientific Advisory Committee members, no healthcare provider contact information or direct patient identifiers are included. Contact information is not shared outside the Registry.

The patient and infant health information is shared in summary form with the Sponsor and the Scientific Advisory Board, in the Registry Annual Interim or Final Reports, but not in publications or presentations. The information contained in line listing may include dates of exposure, prenatal tests, pregnancy outcome date, and other relevant outcome information.

10.3.2 Access to Data

Registry Staff: The Registry Investigators, data collection and management staff reside at the OTIS Autoimmune Diseases in Pregnancy Project Coordinating Center located at UCSD. These personnel, under the supervision of the Investigators, have access to the physical files and electronic data.

Sponsor: Sponsor representatives will have access to summary data presented in the interim annual and final reports. Any reports of SAEs occurring in prucalopride-exposed pregnancies enrolled in the study (major structural birth defects, spontaneous abortions/miscarriages, elective terminations/abortions, stillbirths, and neonatal/infant deaths) not originating with the Sponsor will be reported to the Sponsor through the MedWatch protocol by the Registry staff, regardless of attribution. Any other AE that is outside the scope of the study, whether serious or not, that the woman or her physician attributes to prucalopride exposure will also be reported to the

Sponsor through a MedWatch form. This data will be utilized by the Sponsor to meet the FDA reporting requirements.

Scientific Advisory Board: The Registry Scientific Advisory Board will receive summary information on pregnancy outcomes for all enrolled in the Registry at each annual interim and final meeting. These reports include specific listings of the specified pregnancy-related SAEs. Contact information is not included in any listings provided. The Scientific Advisory Board, in preparation for the annual meetings, reviews the listings and summary tables. At the meeting, interpretation of results will be discussed and decisions made on the appropriate updates to the Annual Report.

Patient Identifiers: Mother and infant names are obtained as part of the informed consent and linked to pregnancy history, exposure and outcome data from maternal interview, medical records, and physical examinations. This personally identified information is maintained securely at the OTIS Research Coordinating Center and is not shared with the Sponsor, Scientific Advisory Board member, or any external parties other than what is required by law. Data summaries for the Sponsor and Scientific Advisory Board will be provided only when data have been stripped of personal identifiers.

Published Data: Care is taken to assure that a patient is not identifiable in the data tables published in the Annual Interim or Final Reports, or other publications. No protected health information is included in any published information. Ad hoc requests for Registry information are reviewed and approved by the Registry Investigators with the advice of the Scientific Advisory Board.

10.4 Record Retention

The OTIS Research Center will retain study documentation until the end of the study and for a minimum of 25 years after the study completion.

10.5 Premature Discontinuation of the Study

Discontinuation of the Registry will be considered at such time as:

- Sufficient information has accumulated to meet the scientific objectives of the Registry, ie, the target sample size is achieved, or
- Other methods of gathering appropriate information become achievable or are deemed preferable, or
- The feasibility of collecting sufficient information diminishes to unacceptable levels because of low exposure rates, poor enrollment, or losses to follow-up
- Prucalopride is withdrawn from the market in the US
- In the case that discontinuation or termination of the study is deemed necessary and appropriate, the Sponsor and the Registry Investigators will notify the IRB and FDA, and any other regulatory agencies as needed.

10.6 Audits and Inspections by Regulatory Agencies

The Investigator agrees to allow any competent regulatory authority such as federal agencies (eg, FDA), upon their request, to inspect all premises where the project is or has been performed. Upon receipt of the health agency request to inspect its premises as it relates specifically to the performance of the project, the sponsor will be notified promptly.

The Investigator will make every effort to help with the performance of any federal audits and inspections, giving access to all necessary facilities, data, and documents. The confidentiality of the data verified and the protection of the study participants will be respected during these inspections. Any result and information arising from the inspections by the competent authorities will be communicated by the OTIS Research Center to the Sponsor. OTIS shall take appropriate measures required to take corrective actions for all problems found during the audit or inspections by a federal agency.

10.7 Responsibilities

10.7.1 Scientific Advisory Board

An external Scientific Advisory Board is convened by the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) under the direction of Dr. [redacted] and the American Academy of Allergy, Asthma and Immunology. The VAMPSS Advisory Board, under the VAMPSS charter, will review the Registry summary data on an annual basis. Members of the Board will provide advice to the Registry Investigators on interpretation of the data and provide advice on strategies for the dissemination of information regarding the Registry. A final annual interim report will be prepared after each meeting to summarize these aggregate data and a final report will be issued at the end of the study. The VAMPSS Scientific Advisory Board is chaired by a designated member of the Board.

10.7.2 Sponsor

The Sponsor provides financial support for the Registry and will support referrals to the Registry. The Sponsor will work with the Registry Investigators to ensure that objectives are being met, and that the Registry staff is assisting the Sponsor in meeting its regulatory reporting responsibilities. The Sponsor will be responsible for SAE reporting to the regulatory authorities for their specific product.

10.7.3 Study Investigators and Research Coordinating Center

The OTIS Research Coordinating Center is responsible for the collection, management, and follow-up of the reports of pregnancy exposures to the Registry, conducting the analysis of the data, updating of the Registry Annual Interim and Final Reports, interpretation of the findings, and preparation of publications resulting from the Registry. In addition, the Research Coordinating Center will schedule, plan, and conduct Scientific Advisory Board meetings, and forwards reports of major structural birth defects, spontaneous abortions/miscarriages, stillbirths, elective terminations/abortions or neonatal/infant deaths occurring in prucalopride-exposed pregnancies enrolled in the Registry to the Sponsor within 24 hours of becoming aware of the event. The Research Coordinating Center is responsible for increasing awareness of the Registry

through direct mailings, contacting groups, and organizations who might be sources of referrals, and promoting the project at professional meetings, social media, as well as presenting results in abstracts and publications in scientific journals. The Research Coordinating Center is also responsible for communicating final results of the cohort study to the study participants.

The Project Investigators from the Research Coordinating Center are responsible for the conduct of the Registry. Project management activities include, managing the Research Coordinating Center staff and activities, analysis of data that is collected as part of the Registry, development of reports and other publications, maintaining current IRB approval, and communicating with the Sponsors and the Scientific Advisory Board who will meet at least on an annual basis.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS

All adverse events will be managed and reported in compliance with all applicable regulations and Takeda policies for reporting of adverse events (AEs) and product complaints.

11.1 Definitions

An **adverse event** is any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with use of the product, whether or not related to the product. Worsening in severity of a pre-existing condition after administration of the product would be considered an AE.

Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for an SAE.
- A laboratory test result that requires the subject/patient to receive specific corrective therapy
- A laboratory abnormality that leads to discontinuation of therapy
- A laboratory abnormality that the health care provider considers to be clinically significant

A **serious adverse event** is any untoward medical occurrence that at any dose:

- Results in death. Note that death is an outcome of an event. The event(s) causing death should be recorded; or .
- In the view of the Health care provider, places the subject/patient 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 or;
- Results in persistent or significant disability/incapacity or;
- Is a congenital anomaly/birth defect;

An SAE may also be any other medically important event that, in the opinion of the health care provider, may jeopardize the subject/patient or may require intervention to prevent one of the other outcomes listed in the definition above.

A **product quality issue** (PQI) refers to defects related to the safety, identity, strength, quality, or purity of the product or with the physical characteristics, packaging, labeling, or design of the product.

A **special situation report** (SSR) includes any of the following events:

- Overdose: All information of any accidental or intentional overdose
- Drug abuse, misuse or medication error: All information on medicinal product abuse, misuse or medication error (potential or actual)
- Suspected transmission of an infectious agent: Suspected (in the sense of confirmed or potential) transmission of an infectious agent by a medicinal product.
- Lack of efficacy of Takeda Product
- Accidental/Occupational exposure
- Use outside the terms of the marketing authorization, also known as "off-label"
- Use of falsified medicinal product
- Use of counterfeit medicinal product
- Drug-drug interactions and drug-food interactions
- Inadvertent or accidental exposure with or without an AE
- Unintended benefit

An SSR shall be reported even if there is no associated AE, in accordance with reporting procedures described in Section 11.3.

Relationship Categorization: The process for relationship categorization is further described in Section 11.2.4.

Assigning a relationship of an AE to prucalopride is based on the consideration of all available information about the event, including the temporal relationship to drug administration, recognized association with drug product/class, pharmacological plausibility, and alternative etiology (eg, underlying illness, concurrent conditions, concomitant treatments).

- *Related (Yes):* An AE that follows a reasonable temporal sequence from administration of the prucalopride (including the course after withdrawal of the medication), and for which a causal relationship is compelling enough and/or follows a known or suspected response pattern and the event cannot be explained by the subject's other underlying diseases, complications, concomitant drugs and concurrent treatments.
- *Not related (No):* An AE that does not follow a reasonable temporal sequence from administration of the prucalopride and/or that can reasonably be explained by other factors, such as the subject's underlying disease, complications, concomitant drugs and concurrent treatments.

Identifiable safety information includes any SAE, AE, SSR, or PQI where the Takeda product is known and at least one demographic is known for reporter and the patient.

Takeda awareness date is the date when any person working on behalf of Takeda whether as an employee, consultant, contractor, or in any other capacity becomes aware of a safety information irrespective of whether the information becomes known during a weekend or public holiday.

Medical and scientific judgment shall be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

11.2 Collection of AEs, SAEs, SSRs, and PQIs

Serious AEs (Section 11.1) that are not systematically collected per the study protocol may be reported as spontaneous reports (European Medicines Agency (EMA) guideline on good pharmacovigilance practices (GVP) module VI, section VI.B.1.2. (EMA, 2017).

The following events will be collected and reported to Takeda within 1 business day :

- Serious AEs that are systematically collected per protocol (Section 11.2.1).
- Any event (AE, SAE, SSR, and PQI) that is specifically attributed to prucalopride by the reporter, regardless of seriousness

The OTIS Research Center may be contacted by Takeda to obtain additional information on the event or for data clarification. OTIS Research Center shall make their best effort to obtain the requested additional information and will notify Takeda within 1 working day of obtaining the additional information for a fatal or life-threatening SAE, within 4 calendar days for other SAEs, and within 7 calendar days for all other events/issues.

11.2.1 Pregnancy and Outcomes in a Patient Exposed to Prucalopride

The following safety events are systematically collected to meet the objectives of the registry. The OTIS Research Center will report to the Sponsor within 24 hours of becoming aware of any of the below listed events occurring in any enrolled pregnancy with prucalopride exposure.

The MedWatch form will be used to report these events:

- Pregnancy ending in spontaneous abortion/miscarriage
- Pregnancy ending in stillbirth
- Pregnancy ending in elective termination/abortion
- Major structural birth defect in the fetus or infant
- Hospitalization in infants up to 1 year of age
- Hospitalization of the mother not associated with / related to pregnancy
- Death of infant
- Death of mother

Other pregnancy-related AEs that are study outcomes, such as preterm delivery, will be summarized in the annual interim reports and the final study report.

11.2.2 Adverse Event Information not Collected

The European Medicines Agency (EMA) guideline on good pharmacovigilance practices (GVP) module VI section VI.C.1.2.1.1. accommodates for specific protocol-defined events for which reporting is not required (EMA, 2017). *Pregnancy and breastfeeding* (defined as a SSR in Section 11.1) will not be reported because pregnancy is an eligibility requirement, and breastfeeding is a study variable and an expected occurrence in this population.

11.2.3 Non-serious Events

Non-serious events (unless attributed to prucalopride by the reporter) will not be collected. The registry has frequent contact with the mother for data collection, and all study data are collected through maternal interview(s), medical records, and a pregnancy exposure diary. During the course of data collection, non-serious events (solicited or unsolicited) that are common and expected during normal pregnancies and infancy may be communicated to registry staff.

The justification for not collecting these non-serious events is, as follows:

Outside the scope of the registry. This registry protocol was developed primarily to fulfill a postmarketing requirement with the overall goal of identifying an unexpected serious risk of the long-term safety of prucalopride in women exposed during pregnancy, including assessing risks of pregnancy complications, and adverse effects on the developing fetus and neonate (FDA, 2018). Specifically, the registry is designed to detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. Protocol-specified events will be systematically collected and assessed relative to the comparator in the interim and final analyses and/or evaluated as potential confounders (Section 7.5.3). Safety data obtained from this registry will supplement information received from analyses of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA (FDA, 2018).

Reporter burden. Additional data collection efforts required to characterize non-serious events may increase reporter burden. Streamlining data collection processes and establishing and maintaining a longitudinal relationship between participant and interviewer are recommended to improve participant retention and minimize losses to follow-up (FDA, 2019). Reducing reporter burden is particularly important for voluntary pregnancy registries in which the mother is the primary reporter who may be balancing work and childcare responsibilities (FDA, 2019).

Other reporting avenues. The mother, associated healthcare professionals, and caregivers shall be informed of the possibility to report directly to the relevant Takeda Pharmacovigilance department or national pharmacovigilance reporting system any adverse events not being collected as part of the study. These will be treated as spontaneous reports and independent of the study.

11.2.4 Relationship to Prucalopride

Assessment of causality. Upon receipt of events submitted to Takeda by the registry, Takeda will assess relationship based on available information. The OTIS Research Center may be contacted by Takeda to obtain additional information on the event or for data clarification.

The justification for not conducting a relationship assessment at the site is as follows:

A lack of evidence on human pregnancy exposures to evaluate relationship. For most medications, pregnant women are actively excluded from clinical trials. Consequently, at the time of the initial marketing, there may be no human reproductive toxicity data to inform the safety of a medication taken during pregnancy (FDA, 2019). Therefore, it is the goal of the registry to assess the relationship of targeted safety endpoints to prucalopride in a comparative analysis of exposed and unexposed pregnant women.

No direct interaction with participant. In this call center-based study, maternal interview(s), medical record reviews, and a pregnancy exposure diary are the only data sources. Other than telephone interviews, registry personnel have no direct contact with the mother or infant, do not provide any type of healthcare, and have limited information on medical history and comorbidities. Thus, the registry has inadequate information to assign relationship to prucalopride. A Scientific Advisory Committee will review the data annually and adjudicate reports of birth defects, indicated by MACDP coding in the study database. Adverse events collected in this study will be reported in aggregate in the interim and final study reports, which are submitted to the FDA annually (AHRQ, 2014).

No direct contact with healthcare providers. Healthcare providers may contact the Registry and refer patients; however, in all cases the mother is the individual who provides informed consent for participation and completes the interview-based data collection. Health care providers are only contacted when asked to submit copies of medical records.

11.3 Reporting of AEs to Regulatory Agencies and IRB/EC

11.3.1 Obligations of the OTIS Research Center

During the course of the study, the OTIS Research Center will communicate all reportable safety information (as defined in Section 11.2 and Section 11.2.1), serious or not, to Takeda within one business day (but not to exceed 3 calendar days if received before a weekend or a holiday) of the awareness date to the appropriate contact (Section 11.3.2). The regulatory clock for reporting of safety information to Takeda begins when any person associated with this study becomes aware of identifiable safety information. OTIS does not submit MedWatch forms to the FDA. Takeda is responsible for subsequently reporting serious and non-serious events suspected of being related to Takeda products to regulatory authorities. OTIS is responsible for reporting adverse drug reactions to the IRB, if required by national law or regulation, within the timelines required by such law or regulation.

The investigator shall maintain records of all such submissions. A listing of all reported events will be maintained by OTIS and reviewed frequently with the Sponsor throughout and at the end of the study for review and reconciliation.

11.3.2 Reporting Contacts

Adverse events reports and SSRs shall be sent to the following contacts

- Phone : [redacted]
- Email : [redacted]
- Fax : [redacted]

Product and Quality Complaints shall be sent to:

- Phone: [redacted] (US-only)
- Email: [redacted]

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A final report describing the study outcomes will be prepared by the Registry and provided to the Sponsor. The Sponsor will communicate the results to the FDA, and any other relevant regulatory authorities.

12.1 Ownership and Use of Data and Study Results

The Annual Interim and Final Reports produced by the study are jointly owned by OTIS and the Sponsor. The raw study data are owned by OTIS, but accessible by Health Authorities directly in case the Sponsor receives the request of an inspection and/or audit from any regulatory agencies.

The VAMPSS Scientific Advisory Board will have full access to the annual interim reports and the final study report. Specific requests from the Committee for additional analyses or clarifying questions will be addressed by the OTIS Research Center.

12.2 Publications

Publications including manuscripts on the study outcomes will be prepared by the Registry Investigators and provided to the Sponsor for comment. Manuscripts will be provided for comment at least 60 days in advance of planned submission. Abstracts and presentations will be provided for comment at least 30 days prior to planned submission.

The Registry will initiate presentations at scientific and professional meetings. The Registry will use these meetings and several other strategies to raise awareness of the Registry. However, the Registry will not identify individual subjects or share its list of providers.

Interim Reports: An annual interim report will be issued to the Sponsor and the VAMPSS Scientific Advisory Board on an annual basis in conjunction with the annual Advisory meeting. Each issue will contain historical information as well as new data, and therefore will supersede all previous reports. The report will describe the experience of the ongoing study, summarize all reports to the Registry, and provide descriptive data on pregnancy outcomes in this Registry.

Website: Information on the Registry is incorporated into the existing OTIS website that includes a description of the Registry, contact information, enrollment eligibility and instructions (https://mothertobaby.org/pregnancy-studies/). The FDA Pregnancy Registry website will continue to list the OTIS Autoimmune Diseases in Pregnancy Project. The Registry will be posted to ClinicalTrials.gov. The VAMPSS website managed by the American Academy of Allergy, Asthma and Immunology will also contain information about the study. There are other websites that may provide Registry contact information. The Sponsors' websites will maintain links to the Registry website.

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Appendix 1 American College of Gastroenterology Diagnostic Criteria Chronic Constipation

Chronic constipation is defined as the presence of one or both of the following symptoms occurring over a period of at least 3 months:

- Infrequent stools
- Difficult stool passage, including
    - Straining
    - A sense of difficulty passing stool
    - Incomplete evacuation
    - Hard/lumpy stools
    - Prolonged time to stool
    - Need for manual maneuvers to pass stool