QUVIVIQ® (daridorexant)

Insomnia Disorder

Protocol ID-078A403

QUVIVIQ® Pregnancy Registry

Study Phase:	Phase 4
Document type:	Global protocol
Document status and version:	Final Version 4
Date:	23 October 2023
Number of pages:	90
Document number:	D-23.335

IDORSIA AND CRO CONTACT DETAILS

SPONSOR CONTACT DETAILS

SPONSOR	Idorsia Pharmaceuticals Ltd Hegenheimermattweg 91 CH-4123 Allschwil Switzerland ☎ +41 58 844 00 00

CONTRACT RESEARCH ORGANIZATION

CRO	IQVIA 25 Thomson Place Floor 5 Boston, MA 02210 United States ☎ +1 919 998 2000

SIGNATURE PAGE FOR IDORSIA PHARMACEUTICALS LTD

Hereinafter called Idorsia

Indication

Insomnia disorder

Protocol number, study title

ID-078A403 QUVIVIQ® Pregnancy Registry

I approve the terms and conditions relating to this study as defined in this protocol. I confirm that the information contained in this protocol is consistent with the current risk-benefit evaluation of QUVIVIQ, and with the ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines.

TITLE	NAME	DATE	SIGNATURE
PPD	PPD MD	PPD	PPD
PPD	PPD PPD MSc	PPD	PPD

INVESTIGATOR/INSTITUTION SIGNATURE PAGE

Indication

Insomnia disorder

Protocol number, study title, version

ID-078A403, QUVIVIQ® Pregnancy Registry, Version 4

I agree to the terms and conditions relating to this study as defined in this protocol and any other protocol-related documents.

NAME	COUNTRY	TOWN	DATE	SIGNATURE

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND ACRONYMS

AE	Adverse event
Apgar	Appearance, pulse, grimace, activity, and respiration
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CC	Coordinating center
CFR	Code of Federal Regulations (US)
CI	Confidence interval
CRO	Contract research organization
eCRF	Electronic case report form
EDC	Electronic data capture
EEA	European Economic Area
EU	European Union
EUROCAT	European Surveillance of Congenital Anomalies
FDA	Food and Drug Administration (US)
HCP	Healthcare provider
ICF	Informed consent/assent form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LMP	Last menstrual period
MACDP	Metropolitan Atlanta Congenital Defects Program
MedDRA	Medical Dictionary for Regulatory Activities
NI	Non-inferiority
ORA	Orexin receptor antagonist
PI	Principal investigator
PRAC	Pharmacovigilance Risk Assessment Committee
SAE	Serious adverse event
SAP	Statistical analysis plan
US	United States

PROTOCOL SYNOPSIS

TITLE	QUVIVIQ® Pregnancy Registry
RATIONALE AND BACKGROUND	Pregnant women were not enrolled in the clinical development program of QUVIVIQ. However, one subject who became pregnant during a clinical trial and who was exposed to daridorexant during the PPD trimester has delivered a normal full-term baby. Therefore, there are limited data on the use of QUVIVIQ in pregnant women. This registry is intended to provide safety information on maternal, fetal, and infant outcomes of women exposed to QUVIVIQ any time from within 5 half-lives prior to conception through their pregnancy.
RESEARCH QUESTION AND OBJECTIVES	This study will primarily investigate pregnancy, neonatal, and infant outcomes among women with insomnia exposed to QUVIVIQ who are pregnant at time of enrollment and for whom the outcome of the pregnancy is not known at the time of enrollment (this group of women will be referred to as having prospective pregnancies). In the primary analysis, women with insomnia exposed to QUVIVIQ during pregnancy or within 5 half-lives prior to conception (Cohort A) will be compared to a cohort of women unexposed to QUVIVIQ but exposed to other, non-orexin receptor antagonist (ORA) medications for insomnia during pregnancy or within 5 half-lives of the respective insomnia medication prior to conception. (Cohort B1). Additionally, in a secondary analysis, women in Cohort A will be compared to a comparator cohort of women who had no exposure to any insomnia medication during pregnancy and within 5 half-lives of any insomnia medication taken prior to conception (Cohort B2), as well as the overall comparator cohort (Cohort B). Women who were exposed to QUVIVIQ during pregnancy or within 5 half-lives prior to conception, but for whom the outcome of pregnancy is known prior to enrollment (retrospective pregnancies), will be enrolled in this study and analyzed in a separate case series.

STUDY DESIGN	This is an international, longitudinal, observational study. The women's health and obstetric history, adverse events (AEs), pregnancy complications, pregnancy outcomes, malformations of their offspring, and other infant outcomes will be collected. The infants will be followed for 52 weeks after birth. The maximal study duration per woman is 21 months.
PLANNED DURATION	Approximately 10 years from study start (2023) to closure of study (2033). If the target sample size has not been achieved within 10 years, an extension of the study duration will be considered.
SITES/COUNTRIES	The United States, Canada, and countries in the European Economic Area will be included, at a minimum. Depending on local requirements from health authorities, patients from other countries may be included in the registry.
STUDY SIZE	204 pregnant women exposed to QUVIVIQ (Cohort A), 387 pregnant women exposed to other non-ORA medications (Cohort B1), and 194 pregnant women with no exposure to any insomnia medication (Cohort B2) are targeted for enrollment.

	The sample size was estimated to ensure sufficient power to compare the prevalence of major congenital malformations in the infants of women exposed to QUVIVIQ (Cohort A) to infants of women exposed to other non-ORA medications for insomnia (Cohort B1) in the primary analysis using a non-inferiority testing approach. Assuming exposure in the first trimester of pregnancy, a general population prevalence of major congenital malformations of 3% among women in Cohort B1, and an expected prevalence of major congenital malformations of 3.15% among women in Cohort A, an estimated 102 pregnancy outcomes in Cohort A and 204 in Cohort B1 (1:2 ratio) would provide 80% power to rule out a difference represented by a risk ratio of 3.0 or higher in major congenital malformations at a one-sided significance level of $\alpha = 0.025$. Assuming a 15% attrition rate, a live birth rate of 62%, and that 5% of patients in Cohort A will be excluded from the primary analysis due to exposure to insomnia medications other than QUVIVIQ, a minimum of 204 women will need to be enrolled in Cohort A and 387 in Cohort B1.
STUDY POPULATION	A woman must meet the following criteria to be eligible for enrollment: **Prospective pregnancies:** ***Inclusion criteria*** • Diagnosis of insomnia disorder prior to pregnancy. • Pregnancy is ongoing and outcome of pregnancy (i.e., pregnancy loss or live birth) is not known. • One of the following: – Woman exposed to QUVIVIQ at any time during the current pregnancy or within 5 half-lives prior to conception. – Woman exposed to other, non-orexin receptor antagonist (ORA) medications for insomnia during pregnancy or within 5 half-lives of the respective insomnia medication prior to conception. – Woman unexposed to an insomnia medication during pregnancy and within 5 half-lives of any insomnia medication taken prior to conception.

	• Able and willing to consent to the conditions and requirements of the registry. If the patient is a minor, able and willing to consent/assent according to local regulations. • Agrees to electronically sign the Release of Medical Information Form permitting the study staff to contact her healthcare providers (HCPs) (e.g., primary care provider, insomnia specialist, psychiatrist, obstetrician, nurse midwife) and the infant's HCP (e.g., pediatrician) for medical information. ***Exclusion criteria*** • Exposure to any ORA other than QUVIVIQ (including BELSOMRA® (suvorexant), DAYVIGO® (lemborexant), any ORA newly approved during the study period, or any ORA in pre-market clinical studies) during the current pregnancy or within 5 half-lives of the respective medication prior to conception. • Woman is currently participating in an interventional study or has taken an investigational product within 3 months prior to conception or during the current pregnancy. **Retrospective pregnancies:** ***Inclusion criteria*** • Diagnosis of insomnia disorder prior to pregnancy. • Pregnancy has ended. • Woman exposed to QUVIVIQ during pregnancy or within 5 half-lives prior to conception. • Able and willing to consent to the conditions and requirements of the registry. If the patient is a minor, able and willing to consent/assent according to local regulations.

	• Agrees to electronically sign the Release of Medical Information Form permitting the study staff to contact her HCPs (e.g., primary care provider, insomnia specialist, psychiatrist, obstetrician, nurse midwife) and the infant's HCP (e.g., pediatrician) for medical information. ***Exclusion criteria*** • Exposure to any ORA other than QUVIVIQ (including suvorexant, lemborexant, any ORA newly approved during the study period, or any ORA in pre-market clinical studies) during pregnancy or within 5 half-lives of the respective medication prior to conception. • Woman participated in an interventional study or took an investigational product within 3 months prior to conception or during the pregnancy.
DATA COLLECTION ELEMENTS	The data will be provided by the patients, their HCPs and the infant's HCPs, as applicable, and the reporters of information will be captured in the electronic case report form. Some data elements (e.g., insomnia diagnosis) will be reported by both the patient and the patient's HCP. Where there is a discrepancy in the information reported, the HCP-reported information will take precedent. The following key data will be collected: **General** • Identification number. • Contact details of HCP at initial contact with the registry. • Date of initial report. • Documentation of informed consent/assent. • Reporter of information (e.g., patient, HCP). • Inclusion/exclusion criteria.

	Maternal information • Age of the women at conception. • Height, weight: pre-pregnancy, current, and follow-up weight, education, race, ethnicity (if permitted by local regulations). • Medical history: genetic disorder, previous pregnancies and their outcome, hypertension, diabetes, seizure disorder, autoimmune disease, lifetime history of psychiatric diseases (e.g., major depression, anxiety, psychotic diseases), known risk factors for adverse pregnancy outcomes, including exposures to known teratogens, history of oncologic disorders, and any previous exposure to chemotherapy and radiotherapy. • Insomnia history including but not limited to the earliest insomnia diagnosis date and duration of insomnia. • Family reproductive history. **Paternal information (collected from the mother at baseline)** • Height, weight. **Current pregnancy** • Date of the last menstrual period. • Ultrasound results for gestational dating. • Prenatal test results. • Number of fetuses. • Complications during pregnancy (including any adverse drug reaction). • Illness during pregnancy (e.g., virus infection). • QUVIVIQ exposure (start/stop date, dosage, frequency, reason for discontinuation, if applicable). • Other medication or biological product exposures (including other insomnia treatment, prescription drugs, over-the-counter products, and supplements; start/stop date, dosage, frequency, indication). • Substance use (e.g., tobacco, alcohol, illicit drugs, marijuana, caffeine).

	• Chemicals and environmental hazards (e.g., radiation). • AEs. **Initial neonatal information** • Pregnancy outcome (live birth, fetal death, miscarriage, early stillbirth, elective termination, and termination for a fetal anomaly). • Sex. • Mode of delivery. • Obstetric complications (e.g., preeclampsia, premature delivery). • Congenital malformations diagnosed at birth or termination. • Congenital malformations diagnosed after birth. • Weight, length, head circumference, Apgar score at birth, gestational age, and breastfeeding information. • Neonatal illnesses, hospitalizations for serious illness, drug therapies, vaccinations. • Death. • AEs. **Follow-up: Infant information (estimated at 12, 26, and 52 weeks of age)** • Feeding behavior (including breastfeeding), weight, length, head circumference, postnatal growth and development. • Congenital malformations diagnosed. • Vaccination information. • Infant death. • Infant illnesses, hospitalizations, drug therapies. • Medication use of nursing mother (including QUVIVIQ). • AEs and serious AEs.

OUTCOMES	**Primary outcome measure** • Occurrence of major congenital malformations. **Secondary outcome measures** • Minor congenital malformations. • Complications during pregnancy (preeclampsia, pregnancy-induced hypertension, preterm labor, gestational diabetes). • Spontaneous abortion (loss of fetus due to natural causes< 20 weeks gestation). • Fetal death or stillbirth (death of a fetus prior to birth or after 20 weeks of gestation). • Preterm birth (< 37 weeks gestation). • Full-term live birth, i.e., infants born maturely (≥ 37 weeks gestation). • Elective termination, i.e., any induced or voluntary fetal loss. • Small for gestational age at birth (birth weight < 10^{th} percentile). • Any other adverse pregnancy outcomes. • Infant mortality (up to the first year of life). • Infant hospitalizations for serious illness (up to the first year of life). • Postnatal growth and development (i.e., social/emotional, language/communication, neurocognitive, movement/physical development milestones) up to the first year of life.
STATISTICAL ANALYSIS	Retrospective pregnancies will be analyzed in a separate case series with respect to demographic and clinical information and QUVIVIQ exposure (e.g., timing of exposure and duration). In addition, all reported primary and secondary outcomes will be assessed.

	The following analyses will be performed in women for whom the outcome of the pregnancy is unknown at the time of enrollment: • Demographic and baseline disease characteristics will be summarized by cohort. • For the women exposed to QUVIVIQ (Cohort A), the drug exposure will be summarized. • The prevalence of primary and secondary outcome measures will be presented, by cohort, with 95% confidence intervals (CIs) based on the binomial distribution. • Comparative analysis of prevalence of major congenital malformations in Cohort A compared to Cohort B1 (primary analysis) using risk ratio (95% CI). • Comparative analysis of maternal, fetal, and infant outcomes in Cohort A compared to Cohort B (overall and separately for Cohorts B1 and B2) using risk ratio (95% CI). • Sensitivity and subgroup analyses. • Analysis of AEs and SAEs. • External comparator cohort analysis. An interim analysis is planned at 5 years following the first patient enrollment.
ADVERSE EVENT REPORTING	For QUVIVIQ-exposed patients, all adverse pregnancy outcomes (congenital malformations, spontaneous fetal losses, induced abortions), maternal events, and other relevant fetal events, regardless of attribution or seriousness, during pregnancy, breastfeeding, and infant follow-up, as well as a pregnancy form will be sent to Idorsia's Drug Safety Department. Idorsia will perform a reconciliation of the registry database and Idorsia's drug safety database on a regular basis.

MILESTONES	Data collection will start in 2023 and is anticipated to end in 2033. Study progress reports will be submitted annually. An interim analysis will occur in 2028 and the final report will be submitted in 2034. These milestones may be adjusted if the duration of the study is extended beyond 10 years.
ADJUDICATION COMMITTEE	The Adjudication Committee includes individuals with expertise in obstetrics, embryology, teratology, pharmacology, epidemiology, pediatrics, clinical genetics, and insomnia. The Adjudication Committee will make recommendations on data collection and will assist in the review of data and classification of specific pregnancy outcomes.
PRIVACY AND HUMAN SUBJECT PROTECTION	The patient will be requested to sign a consent/assent form to allow the collection of data from the HCPs. The registry protocol, the consent/assent form, and other relevant information will be submitted to the Institutional Review Board or the Independent Ethics Committee, which will ensure that the collection of data and all other procedures associated with the registry are scientifically and ethically sound.
RECRUITMENT STRATEGIES	In order to motivate pregnant women to enroll in this registry, the registry will be announced through various channels/instruments, in accordance with local regulations.

PROTOCOL

1 AMENDMENTS AND UPDATES

Version	Date	Main reason(s)
1	19 August 2022	New.
2	17 April 2023	Changes were made as a consequence of the FDA's comments received on 17 February 2023. In addition, minor changes were made for the purpose of clarification.
3	27 July 2023	Changes were made as a consequence of the FDA's comments received on 16 June 2023 and PRAC comments received on 12 June 2023.
4	23 October 2023	Changes were made as a consequence of the FDA's comments received on 19 September 2023.

2 MILESTONES

Table 1 Study milestones

Milestone	Planned Date
Start of data collection	2023
End of data collection	2033
Study progress reports	Annually[a]
Interim analysis[b]	2028
Final report of study results	2034

[a] Annual study progress reports will align with scheduled safety reporting requirements, 2023–2028.
[b] An interim analysis will be conducted at year 5 of the study to evaluate patient enrollment and estimate sample size for study.

3 RATIONALE AND BACKGROUND

Insomnia is defined as difficulty falling asleep or maintaining sleep; this includes waking during the night or insufficient nocturnal sleep [Thorpy 2012]. The Diagnostic and Statistical Manual of Mental Disorders (5th edition) specifies that to be considered an insomnia disorder, insomnia symptoms must cause impairment of daytime functioning and must occur at least 3 nights per week over the course of 3 months [APA 2013].

The prevalence of insomnia is dependent on the assessment tools and the definition used and is estimated to be between 10–20% in the general population in the US and Western Europe [Ancoli-Israel 2006].

Insomnia causes daytime consequences including excessive sleepiness, low energy, irritability, injuries, motor vehicle accidents, and illness [Nodine 2013]. Sleep loss has also been associated with obesity, diabetes, cardiovascular diseases, hypertension, and an increase in some cancers [Sivertsen 2021].

The fluctuation in pregnancy hormones, including estrogen and progesterone, in conjunction with pregnancy-related symptoms including nausea/vomiting, urination, pain, fetal movements, heartburn, cramps, tingling of legs, and shortness of breath is hypothesized to contribute to insomnia during pregnancy [Nodine 2013, Reichner 2015]. While research is limited, insomnia and sleep loss may be associated with adverse maternal and fetal outcomes, including increased risk of gestational diabetes, cesarean sections, preterm birth, and infants born with a low birth weight [Reichner 2015, Chang 2010]. The effect of sleep medications on pregnancy outcomes is not well understood even though many women are diagnosed with insomnia prior to becoming pregnant. Some medications have the potential to cross the placenta and lead to adverse fetal outcomes.

The purpose of insomnia treatment is to improve sleep onset and sleep duration with a goal to reduce impairments experienced during the day [Lie 2015]. QUVIVIQ (daridorexant), which belongs to the ORA drug class, is a prescription medication for adults with insomnia. In clinical trials, it was found that daridorexant was associated with improvement in sleep onset, sleep maintenance, total reported sleep duration, and daytime functioning when compared to placebo [Mignot 2022]. Pregnant women were not enrolled in the clinical trials of the development program of daridorexant. However, in one Phase 3 trial, a PP year-old woman who became pregnant during the trial, and who was exposed to daridorexant in her PPD trimester, delivered a PPD PPD full-term baby. Therefore, there is limited data on the use of daridorexant in pregnant women.

The goal of this pregnancy registry is to provide safety information on maternal, fetal, and infant outcomes for women who were exposed to QUVIVIQ any time from within 5 half-lives prior to conception through their pregnancy. This registry will monitor the health and safety of these women, and their infants will also be monitored for 1 year.

4 RESEARCH QUESTION AND OBJECTIVES

To investigate pregnancy, neonatal, and infant outcomes in women exposed to QUVIVIQ during pregnancy compared to an unexposed comparator control group.

This study will primarily investigate pregnancy, neonatal, and infant outcomes among women with insomnia exposed to QUVIVIQ who are pregnant at the time of enrollment and for whom the outcome of the pregnancy is not known at the time of enrollment (this group of women will be referred to as having prospective pregnancies). Women with insomnia exposed to QUVIVIQ during pregnancy or within 5 half-lives prior to conception (Cohort A) will be compared to the cohort including women with insomnia who have not been exposed to QUVIVIQ (Cohort B). Cohort B consists of 2 subcohorts. Cohort B1 includes women exposed to other, non-ORA medications for insomnia during pregnancy or within 5 half-lives of the respective insomnia medication prior to conception and is the comparator group for the primary analysis. Cohort B2 includes women who had no exposure to any insomnia medication during pregnancy and within 5 half-lives of any insomnia medication taken prior to conception and will be used as a comparator group for the secondary analysis.

In addition, Cohort A will be compared to women from external groups representing the general population (external comparator).

Furthermore, women who were exposed to QUVIVIQ during pregnancy or within 5 half-lives prior to conception, for whom the outcome of pregnancy was known prior to enrollment (retrospective pregnancies), will also be enrolled in this study but analyzed in a separate case series.

4.1 Primary objective

The primary objective is to compare the prevalence of major congenital malformations among prospective pregnancies in Cohort A and Cohort B1.

4.2 Secondary objectives

The secondary objectives among prospective pregnancies are:

- In women of Cohort A :
  - To estimate the prevalence of pregnancy complications.
  - To estimate the prevalence of adverse pregnancy outcomes.
- In infants of Cohort A:
  - To estimate the prevalence of small for gestational age.
  - To estimate the prevalence of minor congenital malformations.
  - To estimate the prevalence of postnatal growth and development impairment through the first year of life.
  - To estimate the prevalence of infant death through the first year of life.
  - To estimate the prevalence of infant hospitalized for serious illness through the first year of life.

- To compare the prevalence of major congenital malformations of Cohort A to Cohort B2 and to Cohort B.
- To compare maternal, fetal, and infant outcomes of Cohort A to Cohort B, B1 and B2).
- To assess the prevalence of major congenital malformations in Cohort A and in women from external groups representing the general population (external comparator).

The secondary objectives among retrospective pregnancies are:

- To describe the frequency of major congenital malformations, pregnancy complications, adverse pregnancy outcomes, and infant outcomes (including death, hospitalizations for serious illnesses, postnatal growth, and development within the first year of life).

5 RESEARCH METHODS

5.1 Study design

This study is an international, longitudinal, observational study which will collect primary data from pregnant women with insomnia in a standard-of-care setting. In routine care settings, patients are seen regularly by their treating HCPs either for insomnia treatment or for regular assessment after insomnia treatment. Thus, no study-specific visits or evaluations are required by this protocol. The data will be provided by the patients and their HCPs (e.g., primary care provider, insomnia specialist, psychiatrist obstetrician, nurse midwife, other) and the infant's HCPs (e.g., pediatrician) [see Figure 1].

The CC (at least one per country) is responsible for obtaining ICFs from all patients. The CC's PI is responsible for ensuring that ICFs are appropriately obtained by the CC research staff and maintained and filed in accordance with local regulations. The PI will countersign the patient consent form. The CC research staff will record data obtained via questionnaires administered to patients or their HCPs on eCRFs.

The design of this pregnancy exposure registry is consistent with relevant guidelines and recommendations [EMA 2005, HMA 2017, FDA 2019a, Gliklich 2014, ISPE 2008].

Women with prospective pregnancies who have been exposed to QUVIVIQ at any time during pregnancy or within 5 half-lives prior to conception (defined as LMP + 14 days) are assigned to Cohort A. Dosing and treatment duration of QUVIVIQ as part of this observational study is at the discretion of the HCP in accordance with local clinical practice and local labeling.

Women with prospective pregnancies not exposed to QUVIVIQ or any other ORAs (including suvorexant, lemborexant, any ORA newly approved during the study period, or any ORA in pre-marketing clinical studies) will comprise the comparator group (Cohort B). This cohort includes two subgroups of pregnant women defined in more detail below:

- **Exposed to other insomnia therapies cohort (Cohort B1):** women with insomnia exposed to other, non-ORA medications for insomnia during pregnancy [Appendix 3] or within 5 half-lives of the respective insomnia medication prior to conception.
- **Unexposed cohort (Cohort B2):** women with insomnia unexposed to any insomnia medication during pregnancy and within 5 half-lives of any insomnia medication taken prior to conception.

Patients from Cohort B will be enrolled and followed according to the same study procedures and data collection as Cohort A.

Women who were exposed to QUVIVIQ during pregnancy or within 5 half-lives prior to conception, but for whom the outcome of pregnancy is known prior to enrollment (retrospective pregnancies), will be enrolled in this study and analyzed in a separate case series.

Major congenital malformations are the primary outcomes of interest for this study. Other pregnancy, maternal, fetal, and infant outcomes are classified as secondary outcomes.

For women with prospective pregnancies, information on delivery will be collected within 4 weeks of delivery date. Data on risk factors, insomnia treatment exposures, other therapeutic or environmental exposures, and adverse maternal, fetal, and infant outcomes will be collected from patients and their HCPs during pregnancy and through 1 year after birth. Women with retrospective pregnancies will provide retrospective information on exposure and outcomes of interest during their pregnancy.

Major and minor congenital malformations will be classified according to the MACDP and EUROCAT classification system and evaluated by an independent committee of at least 3 qualified, independent teratologists using all available medical records.

Aggregate reports of outcomes will be presented for Cohort A, Cohort B (overall and separately for Cohort B1 and Cohort B2). In addition, the outcomes will be compared with both MACDP and EUROCAT databases. Outcomes among women with retrospective pregnancies will be evaluated in a separate case series.

The sample size (i.e., the number of enrolled patients) was calculated to ensure sufficient power to compare the prevalence of major congenital malformations in the infants of women exposed to QUVIVIQ (Cohort A) with infants of women exposed to other

non-ORA medications for insomnia (Cohort B1) in the primary analysis using an NI testing approach with a one-sided significance level of $\alpha = 0.025$.

Participation in the study is voluntary. Any pregnant woman with insomnia qualifying for either Cohort A or Cohort B or any woman with a retrospective pregnancy, as defined per inclusion/exclusion criteria [see Section 5.2], is eligible for the study. Follow-up will cease in the event of patient loss to follow-up, withdrawn consent, death (mother and/or infant), pregnancy termination, study termination, or end of the registry (whichever comes first).

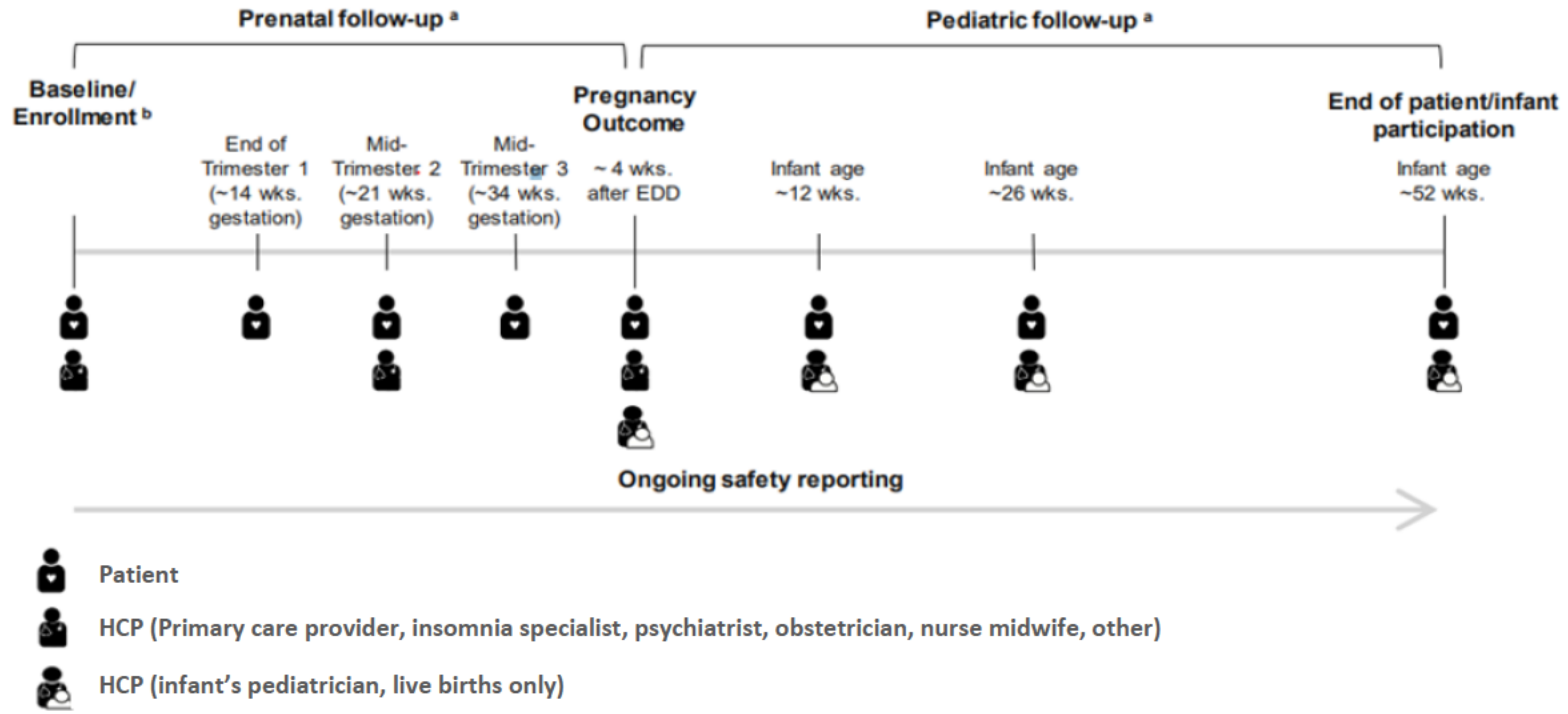
The study start date will be the date from which the first data collection of the first patient is recorded in the study database. The end of the study will be the date from which the last data collected from the last patient is recorded in the study database. The study duration for a patient is up to 21 months and the total expected duration of the study is approximately 10 years. If the target sample size has not been achieved within 10 years, an extension of the study duration will be considered. An interim analysis will be performed at 5 years to evaluate enrollment and to revise sample size, if needed.

The study will be conducted in the US, Canada, and countries in the EEA, at a minimum. Depending on the local requirements of other health authorities, patients from other countries may be included in the registry.

There will be at least 1 CC per country that is responsible for overseeing informed consent from all patients and HCP contacts during the study. See Figure 2 for more information on CC data responsibilities.

Methods to increase registry awareness and enhance patient recruitment and retention are outlined in Section 5.4.5.

Figure 1 Study design schema



[a] Time points of patient and HCP contact shown are based on expected intervals and may vary based on real-world observational data collection. Patient will be contacted if the HCP is unresponsive. The preferred source of information will be the HCP.

[b] Patients with prospective pregnancies must be enrolled prior to the pregnancy outcome (i.e., pregnancy loss or live birth). Patients with retrospective pregnancies will be enrolled after the pregnancy outcome and the data collection schedule will be modified accordingly.

EDD = estimated delivery date; HCP = healthcare provider.

5.2 Study population

Women with insomnia disorder in a standard-of-care setting, and pregnant at time of enrollment, will be prospectively enrolled prior to any pregnancy outcome. Women with insomnia disorder exposed to QUVIVIQ at any time during pregnancy or within 5 half-lives prior to conception will be assigned to Cohort A. Women with insomnia disorder who have been exposed to non-ORA medications for insomnia during pregnancy or within 5 half-lives of the respective insomnia medication prior to conception (Cohort B1) and women with insomnia who have not been exposed to any insomnia medication during pregnancy and within 5 half-lives of any insomnia medication taken prior to conception (Cohort B2) will comprise the comparator group (Cohort B).

Secondary data sources will be used to evaluate the rate of complications in parallel with external comparator cohort(s) representing the prevalence of birth defects in the general population [see Section 5.4.4]. To reduce bias that may occur if outcome information is known prior to enrollment, pregnant women should be enrolled in the study as soon as their pregnancy is known, prior to any informative prenatal testing (such as maternal serum screening or amniocentesis) where the knowledge of the primary study outcome of their pregnancy would be known – either normal or abnormal), and preferably in the first trimester before 20 weeks gestation.

Women who were exposed to QUVIVIQ during pregnancy or within 5 half-lives prior to conception, but for whom the outcome of pregnancy is known prior to enrollment (retrospective pregnancies), will be enrolled in this study and analyzed in a separate case series.

5.2.1 Patient eligibility

Women will be screened for eligibility criteria for each pregnancy, should they contribute more than one pregnancy in the registry. Any within-patient pregnancy correlations will be accommodated in the analysis as part of the SAP.

5.2.1.1 Eligibility criteria for prospective pregnancies

Inclusion criteria

- Diagnosis of insomnia disorder prior to pregnancy.
- Pregnancy is ongoing and outcome of pregnancy (i.e., pregnancy loss or live birth) is not known.
- One of the following:
  - Woman exposed to QUVIVIQ at any time during the current pregnancy or within 5 half-lives prior to conception.
  - Woman exposed to other, non-ORA medications for insomnia during pregnancy or within 5 half-lives of the respective insomnia medication prior to conception.

  - Woman unexposed to any insomnia medication during pregnancy and within 5 half-lives of any insomnia medication taken prior to conception.
- Able and willing to consent to the conditions and requirements of the registry. If the patient is a minor, able and willing to consent/assent according to local regulations.
- Agrees to electronically sign the Release of Medical Information Form permitting the study staff to contact her HCPs (e.g., primary care provider, insomnia specialist, psychiatrist, obstetrician, nurse midwife) and the infant's HCP (e.g., pediatrician) for medical information.

Exclusion criteria

- Exposure to any ORA other than QUVIVIQ (including BELSOMRA® (suvorexant), DAYVIGO® (lemborexant), any ORA newly approved during the study period, or any ORA in pre-market clinical studies) during the current pregnancy or within 5 half-lives of the respective medication prior to conception.
- Woman is currently participating in an interventional study or has taken an investigational product within 3 months prior to conception or during the current pregnancy.

5.2.1.2 Eligibility criteria for retrospective pregnancies

Inclusion criteria

- Diagnosis of insomnia disorder prior to pregnancy.
- Pregnancy has ended.
- Woman exposed to QUVIVIQ during pregnancy or within 5 half-lives prior to conception.
- Able and willing to consent to the conditions and requirements of the registry. If the patient is a minor, able and willing to consent/assent according to local regulations.
- Agrees to electronically sign the Release of Medical Information Form permitting the study staff to contact her HCPs (e.g., primary care provider, insomnia specialist, psychiatrist, obstetrician, nurse midwife) and the infant's HCP (e.g., pediatrician) for medical information.

Exclusion criteria

- Exposure to any ORA other than QUVIVIQ (including suvorexant, lemborexant, any ORA newly approved during the study period, or any ORA in pre-marketing clinical studies) during pregnancy or within 5 half-lives of the respective medication prior to conception.
- Woman participated in an interventional study or took an investigational product within 3 months prior to conception or during the pregnancy.

5.3 Variables

5.3.1 Exposure definition and measures

Exposure information recorded will include start and stop dates, dose, dosing frequency, and reason for discontinuation (if applicable).

The following criteria will be used to assign women to one of the cohorts:

- Cohort A: Exposure to QUVIVIQ at any point during the patient's pregnancy or at any time within 5 half-lives prior to conception.
- Cohort B:
  - Cohort B1: No exposure to QUVIVIQ or any other ORA (including, suvorexant, lemborexant, any ORA newly approved during the study period, or any ORA in pre-marketing clinical studies) but exposure to another insomnia medication [Appendix 3] during pregnancy or within 5 half-lives of the respective medication prior to conception.
  - Cohort B2: No exposure to any insomnia medication during pregnancy and within 5 half-lives of the insomnia medication taken prior to conception.

Women with retrospective pregnancies will be considered to have been exposed to QUVIVIQ if there is documentation of exposure to QUVIVIQ at any point during the patient's pregnancy or at any time within 5 half-lives prior to conception.

Exposure assessments will not be determined for the external comparator cohort(s), as patient-level data is not available; these cohorts represent the prevalence of birth defects in the general population.

5.3.2 Outcome definition and measures

All outcomes defined in this section will be assessed in Cohort A, Cohort B1, Cohort B2, and among women with retrospective pregnancies as patient-level data will be collected [see Table 2]. For the external comparator populations, the outcome of major congenital malformations will be analyzed as described in Section 5.7.4.3.

Table 2 Summary key outcome assessments across data sources

	Prospective pregnancies			Retrospective pregnancies	MACDP and EUROCAT[a]
	Cohort A	Cohort B1	Cohort B2		
Primary Outcome					
Major congenital malformation	X	X	X	X	X
Secondary Outcomes					
Pregnancy complications: preeclampsia, pregnancy-induced hypertension, preterm labor, gestational diabetes	X	X	X	X	
Pregnancy outcomes: preterm birth elective or spontaneous termination, fetal death or stillbirth	X	X	X	X	X[b]
Infant outcomes: minor congenital malformation, size for gestational age, low birth weight, death, hospitalization for serious illness, postnatal growth and development	X	X	X	X	X[c]

[a] Additional external comparator data sources may be used [see Section 5.4.4], but similar to MACDP, only aggregate data will be available for comparison to this registry.
[b] MACDP and EUROCAT contain information on gestational age and birth outcome, if a delivery record is available.
[c] MACDP and EUROCAT contain information on birth weight, if a delivery record is available.
MACDP = Metropolitan Atlanta Congenital Defects Program; EUROCAT = European Surveillance of Congenital Anomalies.

5.3.2.1 Primary outcome

Major congenital malformations

Congenital malformations will be primarily classified according to the MACDP classification system [CDC 2021]. Adjudicated major congenital malformations will serve as the primary outcome in this study (minor malformations will be excluded from the primary analysis). The MACDP classification lists major and minor birth defects that are tracked by MACDP, as well as conditions that are never included and those that are only included under certain circumstances. The code is based on the International Classification of Diseases, 9th Revision, Clinical Modification and the British Paediatric Association

Classification of Diseases. All major congenital malformations will also be classified according to the EUROCAT classification system, if different from MACDP classification.

The CC will obtain medical records from the hospital and/or clinic where the suspected anomaly was identified. The records will be de-identified by the CC and uploaded into the secure IQVIA Clinical Event Validation and Adjudication Endpoint Adjudication System. All documents will be compiled by Clinical Event Validation and Adjudication into a dossier for review by the independent teratologists. All potential major congenital malformations identified by the patient's HCPs or the infant's HCPs will be evaluated by a qualified, independent committee of at least 3 teratologists using all available medical records [see Section 10]. The classification of potential major congenital malformations will be based upon the teratologists' adjudication, who will be blinded to patient exposure status. The adjudication process will involve the classification of congenital anomalies by both MACDP and EUROCAT classification systems.

5.3.2.2 Secondary outcomes

5.3.2.2.1 Pregnancy complications

Preeclampsia

Primary preeclampsia will be based on HCP-reported diagnosis. It is defined as the presence of hypertension on 2 occasions at least 4 hours apart after 20 weeks gestation (in a woman with previously normal blood pressure) and proteinuria; or, in the absence of proteinuria, a new onset of hypertension accompanied by one of the following conditions: thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or cerebral or visual symptoms [ACOG 2019].

Pregnancy-induced hypertension

High blood pressure (elevated: systolic between 120–129 mmHg and diastolic less than 80 mmHg; Stage 1 hypertension: systolic between 130–139 mmHg or diastolic between 80–89 mmHg; Stage 2 hypertension: systolic at least 140 mmHg or diastolic at least 90 mmHg) associated with pregnancy, as diagnosed by the treating HCP [ACOG 2019].

Preterm labor

Preterm labor will be based on HCP-reported diagnosis. It is characterized as regular contractions of the uterus resulting in changes in the cervix that start before 37 weeks of pregnancy. Any interventions or treatments provided to the patient as a result of preterm labor will be collected.

Gestational diabetes

Gestational diabetes will be based on HCP-reported diagnosis. It is characterized by the development of carbohydrate intolerance with first onset or first recognition during pregnancy. A record of an oral glucose tolerance test during pregnancy will also be accepted for data collection, where available [ACOG 2018].

5.3.2.2.2 Pregnancy outcomes

Elective or therapeutic pregnancy terminations

Elective or therapeutic pregnancy terminations are defined as any induced or voluntary fetal loss during pregnancy. If available, data from pathologic examination of the abortus or fetus will be evaluated by the Adjudication Committee [see Section 10] for structural or chromosomal defects. The reason for elective or therapeutic termination will be collected. Elective versus therapeutic terminations will be summarized separately.

Spontaneous abortions

A spontaneous abortion is defined as loss of a fetus due to natural causes at < 20 weeks of gestation. If available, information from gross or pathologic examination of the abortus or fetus will be evaluated by the Adjudication Committee [see Section 10] for structural and chromosomal defects.

Fetal death or stillbirth

Fetal death or stillbirth refers to the death of a fetus prior to birth at or after 20 weeks of gestation. In the event of a stillbirth or fetal death, full pathology details will be requested and examined for structural or chromosomal defects. The final classification between fetal death / stillbirth and spontaneous abortion will be based on gestational age.

Live birth

A live birth refers to a complete expulsion or extraction from its mother of a surviving neonate.

Preterm birth

A live birth will be classified as preterm prior to 37 weeks of gestation according to the CDC definition [cdc.gov_a]. Preterm birth will be categorized as early preterm (< 34 weeks), late preterm (34–36 weeks), and early term (37–38 weeks).

5.3.2.2.3 Infant outcomes

Minor congenital malformations

Congenital malformations will be classified according to the MACDP classification system [see Section 5.4.4.1]. Minor congenital malformations are part of the secondary objectives for this study. All potential minor congenital malformations will be evaluated by at least 3 qualified, independent teratologists using all available medical records [see Section 10].

The classification of potential minor congenital malformations will be based upon the teratologist's adjudication, who will be blinded to patient exposure status. Adjudicated minor congenital malformations will not be included in the analysis of the primary objective. All minor congenital malformations will also be classified according to the EUROCAT classification system, if different from MACDP classification.

Size for gestational age

All live births will be classified as small, appropriate, or large for gestational age using the World Health Organization definition [WHO 1995] of birth weight below the 10th percentile, between the 10th and 90th percentile, and above the 90th percentile for age, respectively.

Low birth weight

An infant with low birth weight will be classified as weighing under 2500 g [cdc.gov_b]. Low birth weight can be subclassified into very low birth weight (< 1500 g) and moderately low birth weight (1500 g to 2499 g).

Infant death

An infant death refers to the death of a live-born infant within the first year of life. Infant deaths will be subclassified as neonatal deaths (≤ 28 days of life) and infant deaths (29 to 365 days of life).

Hospitalization for serious illness

Hospitalizations for serious illness refer to in-patient admissions for treatment of potentially life threatening illnesses among live-born infants within the first year of life. Serious illnesses will be based on HCP-reported diagnosis.

Postnatal growth and development

Domains of developmental milestones (i.e., social/emotional, language/communication, neurocognitive, movement/physical development milestones) by age will be defined by guidelines provided by the CDC [CDC 2019]. As recommended by the CDC, the World Health Organization Growth Charts (suitable for use in the US and EEA from birth to 24 months) will be applied for this study, where infant growth measurements will be used to estimate gender-specific weight-for-length, head circumference-for-age, length-for-age, and weight-for-age percentiles. Other growth charts may be utilized as appropriate (e.g., Fenton Preterm Growth Chart for preterm infants) [Fenton 2013]. Developmental milestones will be collected as part of routine clinical practice with pediatrician-determined results of infant stats (i.e., below, above, or at age-appropriate achievement) in each of the domains listed above. 'Ages and Stages' or similar standardized assessments may be collected for this study if performed as part of routine clinical care – no additional information will be mandated for collection as part of this study.

5.3.3 Covariate definition and measures

5.3.3.1 Baseline covariates

- Patient demographics and characteristics
  - Age of patient (mother) at the time of enrollment.
  - Education level (doctoral or professional degree, master's degree, bachelor's degree, associate degree, postsecondary nondegree award, some college, no degree, high school diploma or equivalent, no formal education credential).
  - Race (American Indian or Alaska Native, Asian, Black or African American, Hawaiian or Other Pacific Islander, White, Other/Unspecified).
  - Ethnicity (Hispanic or Latino and Not Hispanic or Latino) – if permitted by local regulations.
  - Height (cm or in).
  - Weight (kg or lbs.); pre-pregnancy and current weight.
  - BMI (derived from height and current weight).
- Paternal demographics and characteristics
  - Height (cm or in).
  - Weight (kg or lbs).
  - BMI (derived from height and current weight).
- Lifestyle risk factors (before and during current pregnancy)
  - Smoking (current, former, never).
  - Caffeine consumption (Y/N).
  - Alcohol use (Y/N, if Y, number of drinks per week).
  - Illicit drug use (Y/N).
  - Marijuana use (Y/N).
- Current pregnancy information (calendar provided to help recall)
  - Date of the LMP.
  - Date of conception.
  - Gestational age at time of enrollment visit.
  - Estimated delivery date.
  - Date and results of any prenatal tests.
  - Pregnancy complications: physician reported preeclampsia, pregnancy-induced hypertension, preterm labor, gestational diabetes, placenta previa.
  - Pregnancy history.
    - Parity: number of pregnancies carried to a variable gestational age (> 20 weeks).
    - Gravidity: number of pregnancies.
    - Previous preterm birth [for definition, see Section 5.3.2.2.2].
    - Previous spontaneous abortions [for definition, see Section 5.3.2.2.2].

- Previous elective or therapeutic terminations [for definition, see Section 5.3.2.2.2].
- Reason for any elective or therapeutic termination.
- History of congenital malformations.
- Other (specify).

- Surgical and medical history or significant maternal medical conditions other than insomnia.
- Insomnia history including but not limited to insomnia diagnosis date and duration of insomnia disorder.
- Family reproductive history including:
  - Multiple births.
  - Pregnancy complications (i.e., preeclampsia, pregnancy-induced hypertension, preterm labor, gestational diabetes, placenta previa).
  - Congenital malformations.
  - Spontaneous abortions.
  - Preterm births.
  - Chromosomal anomalies.
  - Evidence of developmental delays.
- QUVIVIQ treatment: start and stop dates, dose, dosing frequency, reason for discontinuation, if applicable.
- Current and prior medication use starting at 3 months prior to conception (including all prescription and any other over-the-counter treatments, other insomnia treatments, folic acid and other vitamins, herbal remedies or supplements, vaccinations, or other medications used to treat chronic conditions or comorbidities): start and stop dates, if applicable.
- Safety events that occurred from the date of the LMP to study enrollment: patient AEs and SAEs in Cohort A (following QUVIVIQ exposure) and in Cohort B including event, start date, ongoing or end date, seriousness, severity, relationship to QUVIVIQ, outcome, and action taken.

5.3.3.2 Covariates during follow-up

Covariates to be collected during pregnancy, at delivery, during infant follow-up, and at early termination of study participation (if applicable) are described in Section 5.6.1.

5.3.4 Validity and reliability

Data will be collected from the patient's and infant's HCPs or directly from the patient and entered into the eCRF by trained CC research staff [see Section 5.4.2]. Standard definitions for the classification of pregnancy outcomes have been used and proper citations have been provided, where applicable. Some outcomes, such as pregnancy complications, will rely on the report of a diagnosis (e.g., hypertension) and not individual measurements (e.g., systolic and diastolic blood pressure values). Reliability of the data is subject to what is reported by the HCP and/or patient, and methods to ensure the quality of the data to the greatest extent possible are provided in Section 5.6.2. Published literature can be used for comparison of the distribution and/or frequencies of key covariates.

The primary outcome of major congenital malformations and the secondary outcome of minor congenital malformations will be defined using the standard classifications provided by MACDP and EUROCAT, with an independent review by the Adjudication Committee of teratologists who will be blinded to the patient's exposure status [see Section 10].

5.4 Data sources

5.4.1 Collection of data on the electronic case report form

Patient data are obtained from the patients and their HCPs. The degree of detail and completeness of data collected is dependent on local clinical practice.

5.4.2 Data collection during the observation period

The CC is responsible for overseeing patient enrollment (i.e., determining eligibility and obtaining informed consent and permission for medical form release either over the phone or through the app associated with the website) and all patient and HCP contacts.

After a patient provides consent, the CC research staff will obtain demographic and contact information in addition to baseline information at the time of enrollment. All patient and HCP contact information will be confidential and will remain at the CC. Women with retrospective pregnancies will provide retrospective information on exposures and events during the QUVIVIQ-exposed pregnancy. For pregnancies followed prospectively, and when applicable among retrospective pregnancies, infant HCP contact information will be obtained at the delivery follow-up (estimated within 4 weeks of delivery date). The CC research staff will contact the patient each trimester to ascertain the occurrence of pregnancy outcomes or other events [see Section 5.3.3 for list of variables]. Data collection schedules will be modified as necessary based on the gestational age at enrollment. When permitted by local regulations, patients will also have the option to directly enter data into the eCRF through the website-associated app. All variables collected through the app will be the same as those collected by the CC. Regardless of how the data is collected, all time points for data collection will be the same. Below is a list of expected contact points for data collection with patients and HCPs.

Expected contact with patient (actual contact will depend on the gestational age at enrollment):

- Enrollment.
- End of trimester 1 (approximately 14 gestational weeks).
- Mid-trimester 2 (approximately 21 gestational weeks).
- Mid-trimester 3 (approximately 34 gestational weeks).
- Estimated delivery date plus 4 weeks.
- Birth plus approximately 12 weeks, 26 weeks, and 52 weeks (for live births only).

Expected contact with the patient's HCP:

- Enrollment.
- Mid-trimester 2 (approximately 21 gestational weeks).
- Estimated delivery date plus 4 weeks.

Expected contact with the infant's HCP (live births only):

- Estimated delivery date plus 4 weeks.
- Birth plus 12 weeks.
- Birth plus 26 weeks.
- Birth plus 52 weeks.

After enrollment, for each expected contact time, there will be at least 3 attempts made to contact the patient and/or the HCP via phone, email, fax, and app-based notifications as appropriate, approximately 10 business days apart. If data is obtained after a follow-up interval has passed, the CC research staff will accept and enter the data and continue follow-up of the patient.

If the patient experiences an adverse pregnancy outcome or has an elective or therapeutic termination or a termination of unknown cause, the HCP and the patient will be encouraged to report the outcome to the CC research staff as soon as possible. In the event of an elective or therapeutic termination, spontaneous abortion, fetal death or stillbirth, communication with the patient will cease after pregnancy outcome information has been obtained. Idorsia Drug Safety Department will follow-up on all SAEs, including information about fetal or maternal death, with the patient's HCP.

5.4.3 Loss to follow-up

For study purposes, patients will be considered lost to follow-up if any time-based assessment is missed and the corresponding data have not been received by the CC research staff after making additional follow-up attempts with the patient and/or HCP using all contact methods available (e.g., phone, app-based notifications). At least 3 attempts will

be made up to 4 months after the expected date of the missed assessment. The patient's eCRF will be re-opened if additional information is later obtained. All secondary contacts will also be contacted prior to considering a patient lost to follow-up. All data collected prior to the patient being lost to follow-up will be used for analyses, if possible. For analysis purposes, the date of study discontinuation will be recorded as the date of last contact.

Registry awareness, recruitment, and retention strategies to maximize enrollment and minimize loss to follow-up are described in Section 5.4.5.

5.4.4 External comparator cohorts

External comparators can provide additional context for study results and will be used to descriptively characterize study results, with MACDP report serving as the primary external comparator and EUROCAT serving as the secondary external comparator. These populations will represent the estimated underlying prevalence of major structural or genetic birth defects in the general US and EEA populations, respectively. Only aggregate, population-level data or published reports will be used for description.

5.4.4.1 Metropolitan Atlanta Congenital Defects Program

The MACDP, a population-based tracking system for birth defects (established in 1967) in the US, currently captures approximately 35,000 births per year from 3 metropolitan counties in the Atlanta area [CDC 2021]. MACDP has monitored trends in birth defects rates and has served as a case registry for descriptive, risk factor, and prognostic studies of birth defects. Since 1998, MACDP surveillance has required that any signs or symptoms of a defect in the child be reported before their sixth birthday. In a 2007 report, the MACDP presented data on the prevalence and descriptive characteristics of birth defects, including 67 individual defects, in metropolitan Atlanta, Georgia from 1968 to 2003 [Correa 2007].

Major structural or genetic birth defects affected approximately 3% of births in the US [CDC 2008]. The prevalence estimates of stillbirth in 2006 and 2008 using MACDP data were 8.0 (95% CI: 7.3–8.7) and 7.6 (95% CI: 6.9–8.4) per 1000 live births plus stillbirths [Duke 2014].

5.4.4.2 European Surveillance of Congenital Anomalies

EUROCAT is a European network of population-based registries for the epidemiologic surveillance of congenital anomalies [EC 2022]. Started in 1979, the registry includes over 1.7 million births surveyed annually in Europe from 43 registries in 23 countries. Approximately 29% of the European birth population is covered by this network.

A study using 13 registries from EUROCAT from 1 January 1998 through 31 December 2011, found an overall prevalence of congenital anomaly of 27.3 per 1000 births (range: 19.1–39.3 per 1000 births) [Groen 2017]. Of the 84,387 pregnancies with a known outcome (99.4%), 2.33% pregnancies were stillbirths. The proportion of early neonatal mortality (within 7 days of birth) was 2.37% and the proportion of late neonatal mortality (between 7 days to 27 days of life) was 0.84%.

5.4.4.3 Other potential sources

At the time of final report generation, any existing publicly available data sources (e.g., registries, cohorts) or published study results pertaining to insomnia treatment exposures during pregnancy will be reviewed and considered for a summary of results in addition to this registry, where feasible. No statistical comparisons will be made.

5.4.5 Registry awareness, recruitment, and retention

HCPs who treat patients with insomnia, including investigators involved in the clinical trial with QUVIVIQ, will be informed of the pregnancy registry and asked to refer any patient who becomes pregnant to the registry CC or study website. When local regulations permit, patients will be able to enroll in the study through the app associated with the study website. Patients who do not live in a country where enrollment through an app is permitted, or who prefer to enroll through the CC, can initiate enrollment through the CC via phone or email using the contact details on the study website. After which, the CC research staff will contact potential patients to review the consent procedure and initiate enrollment. Future studies involving QUVIVIQ by Idorsia may provide information about this pregnancy registry and the process of referring any women who become pregnant. Patient or HCP reporting of pregnancy during exposure to QUVIVIQ for inclusion in the pregnancy registry is voluntary. HCPs will be made aware that any potentially eligible patients (either for Cohort A or Cohort B) should be referred to the registry as early as possible, ideally before prenatal testing has been performed. HCPs will also be made aware that any potentially eligible patients with retrospective pregnancies should be referred to the registry. Women with retrospective pregnancies who do not wish to enroll in the registry will be followed by Idorsia according to standard post-marketing pharmacovigilance.

5.4.5.1 Registry awareness

The registry will utilize awareness strategies that were effective in other pregnancy exposure registry programs. Multiple approaches, aimed toward both HCPs and patients, will be used to increase awareness of the registry, such as the study website, the website-associated app, social media, print and electronic media, and scientific conferences. The registry will also be included in labeling and listed on the US FDA Office of Women's Health Pregnancy Registry website. Registry awareness activities and content will be evaluated on a regular basis to ensure target populations are being reached yet minimize any burden on the recipients. Channels for providing feedback on registry

material and correspondence with potential HCPs and patients will be detailed in a Recruitment and Retention Plan.

5.4.5.2 Registry recruitment

Active outreach will occur to obtain reports of women exposed to QUVIVIQ during pregnancy and women with insomnia who may be eligible for the comparator cohorts and receive medical care from the same clinical sites. Outreach efforts may include the following:

- Discussion of the registry with investigators participating in QUVIVIQ clinical studies, with periodic written reminders.
- Notification of the registry to specialists and practitioners who may prescribe QUVIVIQ as well as insomnia education and support groups via the following:
  - Investigator awareness electronic flyer.
  - HCP introduction letters.
- Collection of patient referral information at enrollment (e.g., HCP, website/internet, sponsor, etc.)

Patient recruitment is dependent on several factors. The uptake of new medications like QUVIVIQ is unpredictable and has the potential to impact the feasibility of meeting recruitment targets. In addition, the expected pace of exposure to pregnant women and the willingness of pregnant women to voluntarily participate in a registry are difficult to predict. Continuous monitoring of patient recruitment rates (comparing projects with observed rates) will allow for strategies to be implemented in response to any recruitment challenges.

5.4.5.3 Registry retention

Registry retention efforts may include (but are not limited to) electronic newsletters to HCPs that may include engagement emails, SMS / text messages / email / phone call reminders, notifications through the website and associated app, or ‘thank you’ messages for patients and/or HCPs (where relevant). The projected vs observed dropout rates will be continuously monitored. Retention planning will be performed in advance as part of the Recruitment Risk Management Plan and will include steps to take if the rate of patient completion decreases. These steps to ensure patient recruitment and retention in the registry include an action plan to implement at study start, in addition to an action plan that may be implemented as the study progresses and new enrollment information becomes available. Retention efforts for both HCPs and patients will be documented in the Recruitment and Retention Plan.

5.4.6 Safety data collection

All AEs and SAEs following exposure to QUVIVIQ and in Cohort B will be recorded in the eCRF during the observation period from the LMP through the end of study follow-up (i.e., patient loss to follow-up, withdrawn consent, death [mother and/or infant], pregnancy termination, study termination, or end of the registry [whichever comes first]). HCPs will report maternal and fetal AEs and SAEs occurring during pregnancy and infant AEs and SAEs occurring during the infants first year of life as applicable to the CC research staff, who will enter them in the eCRF. All exposures to QUVIVIQ during pregnancy will be sent via the Idorsia pregnancy form to the Idorsia Drug Safety Department. Any AEs and SAEs following exposure to QUVIVIQ will also be reported to the Idorsia Drug Safety Department. See Section 7 for a full description of safety reporting procedures.

5.5 Study size

5.5.1 Sample size calculation for the primary outcome

The sample size (i.e., the number of enrolled patients) was calculated to ensure sufficient power to compare the prevalence of major congenital malformations in the infants of women exposed to QUVIVIQ (Cohort A) with infants of women exposed to other non-ORA medications for insomnia (Cohort B1) in the primary analysis using an NI testing approach with a one-sided significance level of $\alpha = 0.025$.

Hypothesis:

H_0: $P_A - P_{B1} \geq$ margin versus H_1: $P_A - P_{B1} <$ margin

where

P_A is the probability of major congenital malformations in Cohort A.

P_{B1} is the probability of major congenital malformations in Cohort B1.

The null hypothesis is that P_A is larger than P_{B1} by a margin corresponding to a risk ratio of 3.0:

Risk Ratio = $(P_{B1} + \text{margin}) / P_{B1}$
or margin = P_{B1}*Risk Ratio – P_{B1}

A general population prevalence of major congenital malformations of 3% among women in Cohort B1 is assumed. The NI margin is 3%*3.0–3%=6%.

Assuming a true difference of 0.15% between P_A and P_{B1} (corresponding to a relative increase of 5% from P_{B1}), sample sizes of 102 pregnancy outcomes in Cohort A and 204 events in Cohort B1 achieve 80.1% power to exclude an increase in risk of more than a risk ratio of 3 in Cohort A compared to Cohort B1. The test statistic used is the one-sided Z-test with a significance level of 2.5%. The proportion for the reference group is $P_{B1} = 3\%$

[see Table 3]. Calculations were made by using nQuery V9.1.1.0, module PTE0U-1 [Machin 1987].

The hypothesis testing will be based on comparing the upper bound of the 97.5% one-sided confidence interval for P_A- P_{B1} with the NI margin. If the upper bound is below the NI margin, then noninferiority of A vs B1 will be concluded.

The following formula was utilized to calculate sample size:

$$Na = \frac{(\mathrm{r}+1) * \left(Z_{1-\beta} + Z_{1-\alpha}\right)^2 * \left(\frac{Pa * (1-Pa) + Pb1 * (1-Pb1)}{2}\right)}{\mathrm{r} * ((Pa - Pb1) - margin)^2}$$

$$Nb1 = r * Na$$

where N_A is the number of pregnancy outcomes required in Cohort A, N_{B1} is the number of pregnancy outcomes required in Cohort B1, r is the allocation ratio (Cohort A : Cohort B1, 1:2 ratio), $Z_{1-\beta}$ and $Z_{1-\alpha}$ are the 80% and 97.5% percentiles of the standard normal distribution, respectively.

Sample size estimates with risk ratios varying from 2.0 to 3.0 and with various observed percentages in Cohort A are presented in Table 3.

These numbers are further adjusted with a 15% attrition rate (drop-out or missing data), a live birth rate of 62% [FDA 2002], and assuming that 5% of patients in Cohort A will be excluded from the primary analysis due to exposure to insomnia medications other than QUVIVIQ.

The calculation for the number of enrolled patients needed is as follows:

$$Enrolled\ patients = \sum_{i \in A,B1,B2} \frac{Pregnancy\ outcomes\ needed\ for\ each\ group_i}{Overall\ adjustment\ rate\ for\ each\ group_i}$$

For Cohort A the overall adjustment rate is as follows:

$$(1 - drop\ out\ rate\ ) \cdot (1 - proportion\ of\ pts\ with\ combined\ insomnia\ drugs) \cdot live\ birth\ rate = (1 - 0.15) \cdot (1 - 0.05) \cdot 0.62 = 0.50065.$$

For Cohort B1 and B2 the overall adjustment rate is as follows:

$$(1 - drop\ out\ rate\ ) \cdot live\ birth\ rate = (1 - 0.15) \cdot 0.62 = 0.527$$

The total number of enrolled patients needed in each cohort (Cohort A, Cohort B1 and Cohort B2, respectively) is as follows:

$$Number\ of\ enrolled\ patients =$$

$$\frac{102\ \ (A)}{0.50065} + \frac{204\ (B1)}{0.527} + \frac{102\ (B2)}{0.527}$$

$$\approx 204 + 387 + 194 = 785$$

The number of enrolled patients needed depending on risk ratios varying from 2.0 to 3.0 and depending on expected prevalence of major congenital malformation in Cohort A are presented in Table 3.

Table 3 Sample size calculation

Risk ratio	Assumed prevalence in Cohort B1	Expected prevalence of MCM in Cohort A[a]	NI margin corresponding to the risk ratio	Number of patients to be enrolled by cohort	
				Cohort A with 15% attrition rate, 62% live birth rate, and 5% exposure to insomnia medications other than QUVIVIQ	Cohort B1 with 15% attrition rate and 62%live birth rate
3.0	3.0%	3.0%	6%	192 (Pregnancy outcomes needed: 96)	362 (Pregnancy outcomes needed: 191)
3.0	3.0%	3.15%	6%	204 (Pregnancy outcomes needed: 102)	387 (Pregnancy outcomes needed: 204)
3.0	3.0%	3.3%	6%	218 (Pregnancy outcomes needed: 109)	414 (Pregnancy outcomes needed: 218)
2.75	3.0%	3.0%	5.25%	250 (Pregnancy outcomes needed: 125)	472 (Pregnancy outcomes needed: 249)
2.75	3.0%	3.15%	5.25%	268 (Pregnancy outcomes needed: 134)	509 (Pregnancy outcomes needed: 268)
2.75	3.0%	3.3%	5.25%	290 (Pregnancy outcomes needed: 145)	548 (Pregnancy outcomes needed: 289)

Risk ratio	Assumed prevalence in Cohort B1	Expected prevalence of MCM in Cohort A[a]	NI margin corresponding to the risk ratio	Number of patients to be enrolled by cohort	
				Cohort A with 15% attrition rate, 62% live birth rate, and 5% exposure to insomnia medications other than QUVIVIQ	Cohort B1 with 15% attrition rate and 62%live birth rate
2.50	3.0%	3.0%	4.50%	340 (Pregnancy outcomes needed: 170)	643 (Pregnancy outcomes needed: 339)
2.50	3.0%	3.15%	4.50%	370 (Pregnancy outcomes needed: 185)	698 (Pregnancy outcomes needed: 368)
2.50	3.0%	3.3%	4.50%	401 (Pregnancy outcomes needed: 201)	761 (Pregnancy outcomes needed: 401)
2.25	3.0%	3.0%	3.75%	487 (Pregnancy outcomes needed: 244)	926 (Pregnancy outcomes needed: 488)
2.25	3.0%	3.15%	3.75%	537 (Pregnancy outcomes needed: 269)	1021 (Pregnancy outcomes needed: 538)
2.25	3.0%	3.3%	3.75%	595 (Pregnancy outcomes needed: 298)	1129 (Pregnancy outcomes needed: 595)
2.0	3.0%	3.0%	3.0%	761 (Pregnancy outcomes needed: 381)	1446 (Pregnancy outcomes needed: 762)
2.0	3.0%	3.15%	3.0%	857 (Pregnancy outcomes needed: 429)	1628 (Pregnancy outcomes needed: 858)
2.0	3.0%	3.3%	3.0%	971 (Pregnancy outcomes needed: 486)	1843 (Pregnancy outcomes needed: 971)

[a] Expected prevalence in Cohort A is $P_A = 1.0, 1.05, 1.10 \cdot P_B$, reflecting that the expected prevalence in Cohort A is slightly higher (increase of 0%, 5%, 10%) than the background prevalence in Cohort B.
MCM = major congenital malformation; NI = non-inferiority.

For the secondary analysis (comparison of the prevalence of major congenital malformations in the infants of Cohort A to the infants of Cohort B2), 194 pregnancy

outcomes in Cohort B2 (1:1 ratio Cohort A:Cohort B2) would allow 86% power to rule out a difference represented by a risk ratio of 3.5 or higher in major congenital malformations at a significance level of $\alpha = 0.025$.

If the prevalence observed in Cohort A is lower than 3.15% (expected prevalence), there will be greater power to demonstrate that the rate of major congenital malformations in the infants of patients in Cohort A is not larger than in Cohort B1.

Subject recruitment will be evaluated at each interim review. Interim analyses are planned for the 5th year after the first patient enrolls, and annually thereafter [Section 5.1]. This will include a sample size re-estimation examining the observed prevalence and risk ratio of major congenital malformations in Cohort A compared with Cohort B1 and account for patient recruitment rates and enrollment projects.

Calculations were performed using nQuery version 9.1.1.0 and R version 4.2.2, using the epi.ssninfb function in the package epiR.

5.5.2 Power for secondary outcomes

785 total enrolled women with 408 pregnancy outcomes (102 for Cohort A, 204 for Cohort B1, and 102 for Cohort B2) will have the following power to rule out a difference represented by the risk ratios presented below [Table 4] for each of the secondary outcomes.

Table 4 Power estimates for secondary outcomes

Secondary outcome category[a]	Secondary outcome[b]	P_B (B, B1 and B2)	P_A [c]	Risk ratio	NI margin	Power for A vs B1	Power for A vs B2	Power for A vs B
Pregnancy complications	Preeclampsia[d]	4.6%	4.83%	2.5	6.9%	95.5%	88.4%	97.4%
				3	9.2%	> 99.9%	98.8%	> 99.9%
				3.5	11.50%	> 99.9%	>99.9%	> 99.9%
Pregnancy complications	Hypertensive disorders[e]	3.0%	3.15%	2.5	4.5%	83.2%	71.0%	87.6%
				3	6.0%	97.6%	92.2%	98.7%
				3.5	7.50%	> 99.9%	98.9%	> 99.9%
Pregnancy complications	Preterm labor[f]	3.0%	3.15%	2.5	4.5%	83.2%	71.0%	87.6%
				3	6.0%	97.6%	92.2%	98.7%
				3.5	7.50%	> 99.9%	98.9%	> 99.9%
Pregnancy complications	Gestational diabetes[g]	4.4%	4.62%	2.5	6.6%	94.6%	86.5%	96.7%
				3	8.8%	> 99.9%	98.5%	> 99.9%
				3.5	11.00%	> 99.9%	>99.9%	> 99.9%
Pregnancy outcomes	Elective or therapeutic pregnancy terminations[h]	18.0%	18.90%	2.5	27.0%	> 99.9%	>99.9%	> 99.9%
				3	36.0%	> 99.9%	>99.9%	> 99.9%
				3.5	45.00%	> 99.9%	>99.9%	> 99.9%
Pregnancy outcomes	Spontaneous abortions[i]	11.0%	11.55%	2.5	16.5%	> 99.9%	>99.9%	> 99.9%
				3	22.0%	> 99.9%	>99.9%	> 99.9%
				3.5	27.50%	> 99.9%	>99.9%	> 99.9%
Pregnancy outcomes	Fetal death or stillbirth[j]	1.4%	1.47%	2.5	2.1%	50.8%	39.8%	56.0%
				3	2.8%	75.9%	62.9%	81.0%
				3.5	3.50%	91.7%	82.0%	94.6%

Secondary outcome category[a]	Secondary outcome[b]	P_B (B, B1 and B2)	P_A [c]	Risk ratio	NI margin	Power for A vs B1	Power for A vs B2	Power for A vs B
Pregnancy outcomes	Live birth[c,k]	62.0%	60.1%	2.5	93.00%	> 99.9%	>99.9%	> 99.9%
				3	124.00%	> 99.9%	>99.9%	> 99.9%
				3.5	155.00%	> 99.9%	> 99.9%	> 99.9%
Pregnancy outcomes	Premature birth[l]	11.0%	11.55%	2.5	16.5%	> 99.9%	> 99.9%	> 99.9%
				3	22.0%	> 99.9%	> 99.9%	> 99.9%
				3.5	27.50%	> 99.9%	> 99.9%	> 99.9%
Infant outcomes	Minor congenital malformations[m]	2.0%	2.10%	2.5	3.0%	39.5%	30.9%	43.7%
				3	4.0%	62.5%	50.2%	67.8%
				3.5	5.00%	81.7%	69.5%	86.1%
Infant outcomes	Small for gestational age[n]	10.0%	10.50%	2.5	15.0%	97.7%	92.7%	98.8%
				3	20.0%	> 99.9%	> 99.9%	> 99.9%
				3.5	25.00%	> 99.9%	> 99.9%	> 99.9%
Infant outcomes	Low birth weight[o]	8.5%	8.93%	2.5	12.8%	95.1%	87.7%	97.0%
				3	17.0%	> 99.9%	98.7%	> 99.9%
				3.5	21.25%	> 99.9%	> 99.9%	> 99.9%
Infant outcomes	Infant death[p]	2.9%	3.05%	2.5	4.4%	53.5%	42.3%	58.5%
				3	5.8%	78.6%	66.1%	83.3%
				3.5	7.25%	93.3%	84.7%	95.7%
Infant outcomes	Hospitalizations for serious illness[q]	2.0%	2.10%	2.5	3.0%	39.5%	30.9%	43.7%
				3	4.0%	62.5%	50.2%	67.8%
				3.5	5.00%	81.7%	69.5%	86.1%

Secondary outcome category[a]	Secondary outcome[b]	P_B (B, B1 and B2)	P_A [c]	Risk ratio	NI margin	Power for A vs B1	Power for A vs B2	Power for A vs B
Infant outcomes	Postnatal growth and development[c,r]	6.0%	6.30%	2.5	9.0%	85.0%	73.4%	89.0%
				3	12.0%	98.1%	93.6%	99.0%
				3.5	15.00%	> 99.9%	> 99.9%	> 99.9%

[a] The total population of enrolled patients (n = 785) was used to estimate the power for the secondary outcomes in the pregnancy complications and pregnancy outcomes categories. The number of pregnancy outcomes (n = 408) was used to estimate the power for the secondary outcomes in the infant outcomes category.

[b] Only live births were considered positive outcomes. All other outcomes were considered negative. Because the assumed rate of live birth in Cohort B is high (62%), the estimated rate of live birth in Cohort A for risk ratios of 2.5 or higher corresponds to a rate below 0%, which is not realistic. Therefore, the estimated power is >99.9%.

[c] For negative outcomes, the assumed prevalence in Cohort A is $\mathbf{P_A = 1.05 \cdot P_B}$. For positive outcomes, the assumed prevalence is $\mathbf{P_A = 1 - ((1 - P_B) \cdot 1.05)}$.

[d] Source data: [**Abalos 2013**]

[e] Source data: [**Turner 2017**]

[f] Source data: [**Danforth 2008**]

[g] Source data: [**Behboudi-Gandevani 2019**]

[h] Source data: [**Jones 2017**]

[i] Source data: [**Ammon Avalos 2012**]

[j] Source data: [**Hug 2021**]

[k] Source data: [**Ventura 2000**]

[l] Source data: [**Walani 2020**]

[m] Source data: [**Chimah 2022**]

[n] Source data: [**Sclaudecker 2017**]

[o] Source data: [**Osterman 2023**]

[p] Source data: [**who.int**]

[q] Source data: [**McLaughin 2022**]

[r] Source data: [**Valla 2015**]

NI = non-inferiority; P_A = prevalence in Cohort A; P_B = prevalence in Cohort B.

5.6 Data management

5.6.1 Data collection

The reporter of information can be the patient, patient's HCPs, or infant's HCP, where applicable [see Figure 1]. This information includes all data collection elements described in Section 5.3. Where the HCP is unavailable, the patient can report the necessary information to the CC research staff for entry into the eCRF. Where there is a discrepancy in the information reported by the patient and the HCP, the HCP-reported information will take precedent. In particular, the insomnia diagnosis and history will be collected from both the patient and the HCP (i.e., preferably not the obstetrician or nurse midwife). However, if the HCP cannot be reached to confirm the insomnia diagnosis and history, the patient is considered a suitable source for reporting insomnia history characteristics.

5.6.1.1 Baseline

The baseline information and any data up to the point of enrollment will be collected at the enrollment encounter. Baseline information will be collected to confirm patient eligibility, collect relevant medical history, and characterize the current pregnancy status of the patient. The following data elements will be collected at baseline:

- General
  - Identification number.
  - Contact details of HCP at initial contact with the registry.
  - Date of initial report.
  - Documentation of informed consent/assent.
  - Reporter of information (e.g., patient, HCP).
  - Inclusion/exclusion criteria.
- Maternal Information
  - Age of patient (mother) at conception.
  - Patient demographics and characteristics: height, pre-pregnancy and current pregnancy weight, education, BMI, race, ethnicity (if permitted by local regulations).
  - Medical history: genetic disorder, previous pregnancies and their outcome (parity, gravidity, previous preterm births, previous spontaneous abortions or elective or therapeutic terminations, reasons for any elective or therapeutic termination, history of congenital malformations), hypertension, diabetes, seizure disorder, autoimmune disease, lifetime history of psychiatric diseases (e.g., major depression, anxiety, psychotic diseases), known risk factors for adverse pregnancy outcomes including exposures to known teratogens [Appendix 2], history of oncologic disorders, and any previous exposure to chemotherapy and radiotherapy.

  - Insomnia history including but not limited to the earliest insomnia diagnosis date and duration of insomnia.
  - Family reproductive history (e.g., multiple births, pregnancy complications [i.e., preeclampsia, pregnancy-induced hypertension, preterm labor, gestational diabetes, placenta previa], congenital malformations, spontaneous abortions, premature births, chromosomal abnormalities, evidence of developmental delays).
- Paternal Information (to be reported by the mother)
  - Demographics and characteristics: height, weight, BMI.
- Current pregnancy
  - Date of the LMP.
  - Ultrasound results for gestational dating.
  - Prenatal test results (e.g., rubella titer, toxoplasmosis, venereal disease research laboratory test, hepatitis screen, ultrasounds, amniocentesis, maternal serum alpha-fetoprotein screen, glucose screen).
  - Number of fetuses.
  - Complications during pregnancy (including any adverse drug reaction).
  - Illness during pregnancy (e.g., virus infection).
  - QUVIVIQ exposure (start/stop date, dosage, frequency, reason for discontinuation, if applicable).
  - Other medication or biological product exposures, including other insomnia medications, prescription drugs, over-the-counter products, supplements (start/stop date, dosage, frequency, indication).
  - Substance use (e.g., tobacco, alcohol, illicit drugs, marijuana, caffeine consumption).
  - Chemicals and environmental hazards (e.g., radiation).
  - AEs that occurred from the date of the LMP to study enrollment: patient AEs and SAEs in Cohort A (following QUVIVIQ exposure) and in the Cohort B including event, start date, ongoing or end date, seriousness, severity, relationship to QUVIVIQ, outcome, hospitalization, duration or hospitalization, and action taken.

5.6.1.2 Study follow-up

Women will be followed from enrollment through the end of their pregnancy and up to 52 weeks after the infant's birth. Infants will be followed for 52 weeks after birth. Maternal outcomes during the postpartum follow-up year (aside from safety surveillance and lactation information from breastfeeding mothers) will not be collected. Specific data to be collected during different periods during follow-up are detailed below. Safety reporting will be ongoing throughout the duration of the study.

5.6.1.2.1 During pregnancy follow-up (estimated at approximately 14, 21, and 34 weeks gestation)

- Date of contact.
- Reporter of information (e.g., patient, HCP, other).
- Current weight.
- Changes in lifestyle risk factors (e.g., smoking, caffeine, alcohol use, illicit drug use, marijuana use).
- Insomnia information including but not limited to insomnia improvement.
- Changes in comorbid conditions.
- QUVIVIQ treatment: start and stop dates, dose, dosing frequency, reason for discontinuation, if applicable.
- Current medication (including other insomnia treatments, over-the-counter medications, folic acid and other vitamins, herbal remedies or supplements, vaccinations, or other medication use to treat chronic conditions or comorbidities): start and stop dates, dose, dosing frequencies.
- Ultrasound results for gestational dating.
- Prenatal test results.
- Pregnancy outcome: live births, spontaneous abortions, stillbirths, elective or therapeutic terminations, and autopsy results and pathology reports, if available.
- Reason for elective or therapeutic termination: prenatal testing finding, risk to mother's health, or undesired pregnancy.
- Congenital malformations noted: description and attribution.
- Patient AEs and SAEs in Cohort A and in Cohort B: event, start date, ongoing or end date, seriousness, severity, relationship with QUVIVIQ, hospitalizations, duration of hospitalization, outcome, and action taken.

5.6.1.2.2 At delivery

- Reporter of information (name and position).
- Pregnancy outcome: live births, spontaneous abortions, stillbirths, elective or therapeutic terminations.
- Reason for elective or therapeutic termination: prenatal testing finding, risk to mother's health, or undesired pregnancy.
- Autopsy results and pathology reports, if available.
- Mode of delivery: vaginal delivery, assisted delivery / cesarean section, type of anesthesia.
- Insomnia information including but not limited to insomnia improvement.

- Changes in comorbid conditions.
- QUVIVIQ treatment: start and stop dates, dose, dosing frequency, reason for discontinuation, if applicable.
- Current medications (any other insomnia treatments, folic acid and other vitamins, herbal remedies or supplements, vaccinations, or other medications used to treat chronic conditions or comorbidities): start and stop dates.
- Changes in lifestyle risk factors: smoking, caffeine consumption, alcohol use, illicit drug use, and marijuana use.
- Patient AEs and SAEs in Cohort A and in Cohort B: event, start date, ongoing or end date, seriousness, severity, relationship with QUVIVIQ, outcome, and action taken.
- Infant characteristics.
  - Gestational age at birth.
  - Sex.
  - Birth weight.
  - Length.
  - Head circumference.
  - Birth order (for multiple births) and number of fetuses.
  - Apgar scores 1, 5, and 10 minutes after birth.
  - Congenital malformations noted: description and attribution.
  - Vaccination information.
  - Whether infant is breastfed.
  - Infant medication(s).
  - Neonatal death.
  - Neonatal illness and hospitalizations.
  - Infant AEs and SAEs in Cohort A and in Cohort B: event, start date, ongoing or end date, seriousness, severity, relationship with QUVIVIQ, hospitalization, duration of hospitalization, outcome, and action taken.

5.6.1.2.3 Infant follow-up (estimated at 12, 26, 52, 78, and 104 weeks of age)

- Reporter of information (name and position).
- Feeding behavior (including breastfeeding).
- Weight.
- Length.
- Head circumference.

- Postnatal growth and development (i.e., social/emotional, language/communication, neurocognitive, movement/physical development milestones).
- Evidence of any new congenital malformations and growth alterations since last follow-up.
- Vaccination information.
- Infant death.
- Infant illnesses, hospitalizations, drug therapies.
- Medication use of nursing mother (including QUVIVIQ).
- Infant AEs and SAEs of Cohort A and of Cohort B: event, start date, ongoing or end date, seriousness, severity, relationship with QUVIVIQ, hospitalization, duration of hospitalization, outcome, and action taken.

5.6.1.2.4 Early termination of study participation contact, if applicable:

- Reporter of information (name and position).
- Assessments appropriate for the time of withdrawal.
  - Pregnancy status: gestational age at contact, any prenatal testing performed and results.
  - Pregnancy outcome: live births, spontaneous abortions, stillbirths, elective or therapeutic terminations, and mode of birth.
    - Reason for elective or therapeutic termination: prenatal testing finding, risk to mother's health, or undesired pregnancy.
    - Autopsy results and pathology reports, if available.
    - Infant characteristics: postnatal growth and development, feeding behavior, weight, length, head circumference, breastfeeding status (if infant is breastfed, if the mother was exposed to QUVIVIQ), vaccine information, current medications.
  - Evidence of any new congenital malformations and growth alterations since the last follow-up.
  - Patient or infant AEs and SAEs in Cohort A and in Cohort B: event, start date, ongoing or end date, seriousness, severity, relationship with QUVIVIQ, hospitalization, duration of hospitalization, outcome, and action taken.
- Termination status
  - Completion of follow-up.
  - Early termination/withdrawal (including date of withdrawal, reason for withdrawal).

– QUVIVIQ treatment, current medications (including insomnia medications), pregnancy status, and infant characteristics (for live births), and safety events will be collected similarly as during study follow-up.

5.6.2 Data management

IQVIA, the CRO, will be responsible for the data management of this study. This includes designing the eCRFs with input and final approval from Idorsia, as well as quality checking the accuracy, completeness, and timeliness of data recorded. The CRO will produce a Data Management Quality Plan and a Data Cleaning Plan that describes the quality checking to be performed on the data. Data quality will be enhanced through a series of programmed data quality checks that automatically detect out-of-range or anomalous data. In the event of discrepant data, the CRO will request data clarification from the CC research staff, which the CC research staff will resolve by providing answers in the EDC system.

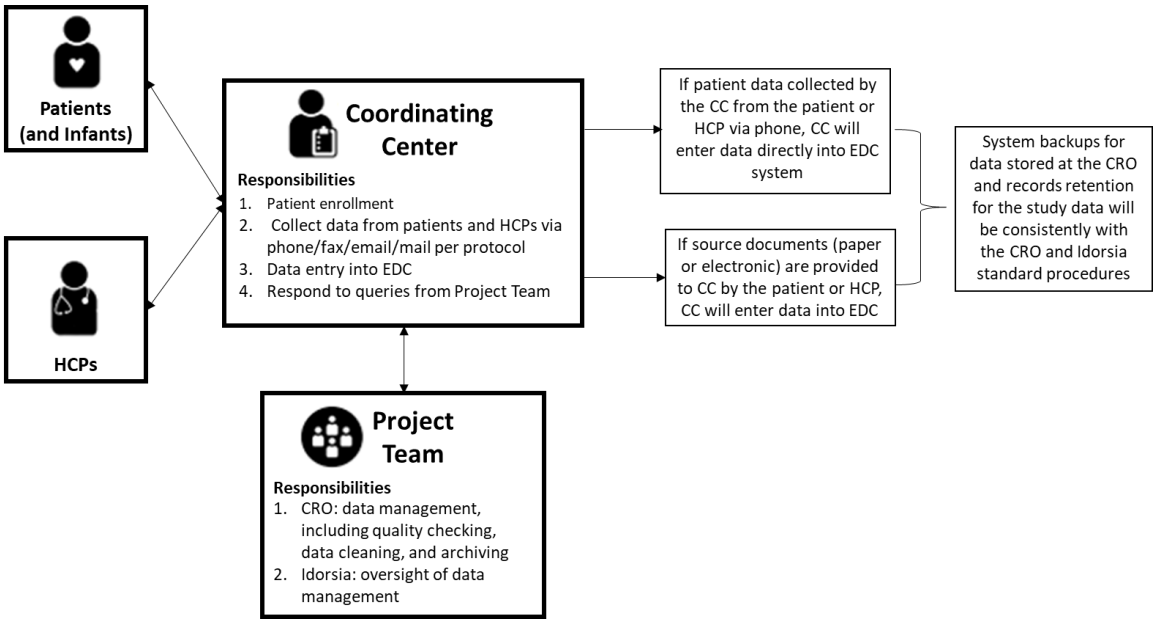
Idorsia will perform oversight of the data management of this study, including the approval of the data management plans and guidance.

The CC, which contains a PI and research staff, will be responsible for data entry into the EDC system. The CC research staff will receive training for reviewing the ICF process with the patient and entering data in the eCRF. The CC research staff will have access to a manual for appropriate eCRF completion. All eCRFs should be completed by designated, trained CC research staff. eCRFs will be reviewed and electronically signed and dated by the PI. In the US, a senior epidemiologist will assume the role of PI, ex-US countries will designate a PI from a site (e.g., HCP).

When permitted by local regulations, patients will also have the option to directly enter data into the eCRF through the website-associated app.

eCRFs and correction documentation will be maintained in the EDC system audit trail. System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO standard procedures. The CRO will comply with Idorsia's procedures regarding archiving and record management.

Figure 2 Data flow overview



CC = Coordinating center; CRO = Contract Research Organization; EDC = electronic data capture; HCP = healthcare provider (e.g., primary care provider, insomnia specialist, psychiatrist, obstetrician, nurse midwife, infant's pediatrician, other).

5.6.3 Source documents

In most cases, the source documents are contained in the patient's medical record and data collected on the eCRF must match the data in the medical records. In some cases, the eCRF, or part of the eCRF, may also serve as a source document. In these cases, a document should be available at the investigator's site and clearly identify the data that will be recorded in the eCRF, and for which the eCRF will stand as the source document. All original source documentation is expected to be stored at the site for the longest possible time required by applicable local regulations.

5.6.4 File retention and archiving

To enable evaluations and/or audits from regulatory authorities or Idorsia, the investigator agrees to keep records, including the identity of all participating patients, all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone call reports). The records should be retained by the investigator according to local regulations, or as specified in the study contract, whichever is longer.

Each site will receive a study site file at study initiation containing all documents necessary for conducting the registry which will be updated throughout the study. This file must be available for review if the site is selected for monitoring, audits, or inspections, and must

be safely archived for at least 5 years after the completion of study participation. Documents to be archived include the patient enrollment log and the signed ICF. If archiving the file is no longer possible at the site, the site is instructed to notify Idorsia.

5.6.5 Changes to the protocol

Changes to the protocol will be documented in written protocol amendments. Major (i.e., substantial or significant) amendments will usually require submission to the relevant IEC/IRB for approval or favorable opinion and the FDA and/or Competent Authorities. In such cases, the amendment will be implemented only after the approval or favorable opinion has been obtained.

Minor (non-substantial) protocol amendments, including administrative changes, will be filed at each participating site and will be submitted to the relevant IEC/IRB or regulatory authorities where required by pertinent regulations. Any amendment that could have an impact on the patient's agreement to participate in the study requires the patient's informed consent prior to continued participation in the study.

5.7 Data analysis

5.7.1 Planned analysis

5.7.1.1 Interim enrollment assessment

Regular study updates will be provided in alignment with required safety reporting requirements and are anticipated annually. At 5 years following the first patient enrollment, an interim analysis will be conducted to assess enrollment and target sample size assumptions, and any needed modifications to patient recruitment and/or retention efforts will be evaluated. A report which summarizes the number of patients enrolled and QUVIVIQ exposure classification information among prospective pregnancies (the proportion of Cohort A vs Cohort B1) and describes primary and secondary outcome data will be included as part of the interim analysis.

5.7.1.2 Final analysis

A final study report will be generated after all data collection is complete, or the study is otherwise terminated, including up to 21 months of follow-up for enrolled women with their child. The final report will encompass all planned analyses, including a description of the complete study population, as described in Section 5.2 and in the SAP.

Details and scope for the final analysis will be described in the SAP.

5.7.1.3 Primary analysis

The final primary analysis will be conducted once all data collection is complete, including up to 21 months of follow-up for enrolled patients. Only women with prospective pregnancies (i.e., outcome of the pregnancy is not known at time of enrollment) will be included in the primary analysis.

The primary outcome for this study is major congenital malformations in infants. All other outcomes will be classified as secondary.

The primary analysis will use risk ratios (one-sided 97.5% CI) to compare major congenital malformations in infants between Cohort A and Cohort B1 among women with first trimester exposure to their respective insomnia medications. Women exposed to QUVIVIQ who take other medications for insomnia at any time during pregnancy will be excluded from the primary analysis. Women with known teratogen exposure during pregnancy will be included in the primary analysis. Sensitivity analyses will be conducted evaluating timing of exposure. Additional sensitivity analyses will be conducted, including women exposed to QUVIVIQ who were exposed to other insomnia medications, and excluding those with known teratogen exposure [Section 5.7.4.4].

Adjudicated major congenital malformations reported up to 1 year of age by the mother or by an HCP will be included in the primary analysis. Pregnant women who receive any prenatal screening after enrollment (post-enrollment) that provides knowledge of the pregnancy outcome will be included in the primary analysis. Decision criteria with regard to prenatal testing before enrollment (pre-enrollment) will be applied to the study population for inclusion in the primary analysis as follows: pregnant women with pre-enrollment prenatal testing who have not received the test results at the time of enrollment will be included in the primary analysis, while pregnant women who had prenatal testing pre-enrollment where the result is known prior to enrollment will be included or excluded from the primary analysis depending on the result of the test (see Table 5 for pertinent descriptions for inclusion in analyses based on timing and the results of prenatal screening tests).

Results from the following prenatal tests will be used to determine if a pregnancy will be included in the primary analysis: maternal serum screening, 18–20-week ultrasound, amniocentesis, chorionic villus sampling, and fetal magnetic resonance imaging. Additional screening tests for major congenital malformations that are adapted in clinical practice during the study period may also be used. Additional exploratory analyses will evaluate major congenital malformation risks among women with exposure in another trimester (e.g., the second and/or third trimester). Women who have received test results (regardless of what the results are) will be included in the primary analysis, except for:

- Women who have received first trimester prenatal screening in which either aneuploid disorders or genetic disorders that cause major congenital malformations have been detected, because these disorders are unrelated to medication use.
- Any prematurity-related disorders and transient conditions.

Table 5 Considered subpopulations of patient groups based on timing and result of prenatal screening tests for inclusion in analysis sets

Groups determined by test and result	Inclusion in analysis
Group 1: Women who had prenatal testing prior to enrollment in registry where the result is known prior to enrollment	Inclusion in each analysis based on subgroup
Subgroup 1: Women who have normal prenatal screening findings	Included in primary analysis; sensitivity analysis of known test result(s) prior to enrollment
Subgroup 2: Women who have pregnancies with aneuploid disorders or genetic disorders that cause major congenital malformations	Excluded from primary and secondary analysis; analyzed as a separate group
Subgroup 3: Women who have pregnancies with results (normal or abnormal) that are unrelated to aneuploid disorders or genetic disorders that cause major congenital malformations	Included in primary analysis; included in sensitivity analysis of known test result(s) prior to enrollment
Group 2: Women who had no prenatal screening prior to enrollment in the registry	Included in primary analysis; included in sensitivity analysis of women who have pregnancies with aneuploid disorders or genetic disorders that cause major congenital malformations
Group 3: Women who had prenatal screening prior to enrollment in the registry and result is not known prior to enrollment	Included in primary analysis; included in sensitivity analysis of women who have pregnancies with aneuploid disorders or genetic disorders that cause major congenital malformations

5.7.2 Planned method of analysis

5.7.2.1 General considerations

Descriptive analyses will be performed to gain an understanding of the qualitative and quantitative nature of the data collected and the characteristics of the sample studied. Continuous variables will be reported as mean (and standard deviation), median, minimum, maximum, and range where appropriate. Categorical variables will be summarized as number and proportion of the total study population, and by subgroups where appropriate.

Data analysis for major congenital malformations will be based on exposure to QUVIVIQ or treatments for insomnia within 5 half-lives prior to conception or the first trimester. The primary analysis set will exclude women who have received first trimester prenatal screening in which either aneuploid disorders or genetic disorders causing major congenital malformations have been detected, because these disorders are unrelated to medication use. Prematurity-related disorders and transient conditions will also be excluded from the analysis of major congenital malformations.

Analyses for the secondary outcomes will be conducted overall (encompassing preconception [within 5 half-lives prior to conception] and the entire pregnancy) as well as separately for preconception and each trimester (first trimester: conception to 13^{+6} weeks' gestation; second trimester: 14^{+0} to 27^{+6} weeks' gestation; third trimester: $\geq 28^{+0}$ weeks' gestation) as sample size allows. See Appendix 4 for the outcome-specific exposure-windows that will be evaluated. Gestational age will be determined based on results from the first available ultrasound or the date of the LMP when an ultrasound is not available [ACOG 2017, EMA 2005].

If sufficient numbers are obtained, analyses will also be presented by the subgroups of maternal age, race/ethnicity, prior history of elective or therapeutic pregnancy termination status, prenatal screening result (positive vs negative), prenatal testing status (performed vs not performed), and other important risk factors [see Section 5.7.4.4].

Any patient who is enrolled in the Cohort A or Cohort B and then becomes exposed to any ORA during pregnancy will be addressed in the analysis depending on the medication, the timing of the exposure, and the outcome of interest.

All computations and generations of tables, listings, and data for figures will be performed using SAS® version 9.4 or higher.

5.7.3 Missing or incomplete data and loss to follow-up

Key strategies for minimizing missing or incomplete data and loss to follow-up for pregnancy registries include activities for registry awareness, recruitment, and retention (of patients and HCPs). Complete details of registry awareness, outreach, and retention efforts will be described in the Recruitment and Retention Plan, and may include the following methods to: 1) increase awareness of the registry by using multiple approaches aimed toward HCPs and patients, such as websites and apps, social media, print media, and scientific conferences; 2) evaluate awareness of the registry periodically; 3) accept data from multiple sources; 4) minimize the burden on HCPs; 5) consistently communicate with HCPs and patients; 6) possibly compensate HCPs; and 7) minimize the burden on patients. Compensation will be considered for patients and/or HCPs, where allowed by local regulations. All activities in this plan will be reviewed on a regular basis and, if needed, changes to the awareness, recruitment, or retention activities or data collection process will be implemented based on the review. The strategies for these activities are described in more detail in Section 5.4.5.

In order to prevent missing data, the following is done:

- Ensuring the primary variables of interest are routinely collected as part of standard-of-care.
- Collecting information via patient reporting, if not collected via HCPs.
- Collecting data elements aligned with study objectives to minimize patient burden.

- Including "not applicable" and "not done" on the CRFs to differentiate from values that are truly unknown.
- Training CC research staff in data collection.
- Planning an interim analysis(es) to characterize enrollment and loss to follow-up to help minimize missing data in the future.
- Checking for missing data patterns and addressing any issues with targeted operational strategies.
- Implementing direct-to-patient strategies to facilitate the capture of patient-reported information.

Should missing data occur, the data will be analyzed as they are recorded in the eCRFs. However, the missing values for data elements will be reported in the annual reports and will be assessed for the likely impact of missing data on the analysis and the pattern of the missing information. Handling of missing data will be described in detail in the SAP.

5.7.4 Analysis sets and groups

5.7.4.1 Baseline descriptive analysis

Patient characteristics are described in Section 5.7.2.1.

Patient disposition characteristics, including summaries for enrolled patients, patients in the analysis set, completers and early withdrawals with the reasons for early discontinuation will be provided. In addition, demographic information (e.g., age, race/ethnicity, BMI), clinical characteristics, including comorbidities and medications, other potential factors that may affect pregnancy outcome, and QUVIVIQ exposure will be described.

5.7.4.2 Analysis of primary and secondary endpoints

The prevalence of major and minor congenital malformations will be calculated using the MACDP convention. If needed for future analyses, minor and major congenital malformations will also be calculated using the EUROCAT convention using the same process. Major malformations will be analyzed separately from minor malformations, with the primary analysis including only adjudicated major congenital malformations. The total prevalence will be calculated by dividing the number of women with any adjudicated cases of each event (observed in live births, fetal deaths, elective or therapeutic terminations, and at any gestational age) by the total number of pregnancies (excluding spontaneous terminations and ectopic or molar pregnancies). The prevalence at birth will be calculated as number of cases observed in live births and stillbirths divided by the total number of births (stillbirths + live births). Data analysis for major congenital malformations will be based on exposure to QUVIVIQ from within 5 half-lives prior to conception through the end of the first trimester.

The prevalence of pregnancy complications, including preeclampsia, pregnancy-induced hypertension, gestational diabetes, and preterm labor, will be summarized by dividing the number of pregnant women with that complication by the total number of pregnant women.

The prevalence of spontaneous abortions will be calculated by dividing the number of women with fetal loss occurring before 20 weeks gestation by the total number of pregnant women.

The prevalence of elective and therapeutic abortion will be estimated similarly as separate outcomes.

The prevalence of preterm birth will be calculated by dividing the number of cases by the total number of births (stillbirths + live births). The prevalence of small for gestational age will be calculated by dividing the number of cases by the total number of live births.

For other events of interest occurring in developing neonates and infants, including mortality, hospitalizations for serious illness, growth, and developmental delays, the prevalence will be calculated as the number of cases divided by the total number of live births.

The prevalence of primary and secondary outcome measures will be presented with 97.5% CIs for binomial proportion. The analyses summarized in this section will be performed on the Cohort A and Cohort B.

The maternal, fetal, and infant outcomes of Cohort A will be compared to Cohort B1 (primary analysis), as well as to Cohort B overall and Cohort B2 (secondary analysis). Additionally, the observed prevalence of major congenital malformations of Cohort A and the external comparator cohort(s) will be assessed.

5.7.4.3 Comparative analyses

Internal comparator analysis

Only prospective pregnancies will be included in the internal comparator analysis. As described in Section 5.7.1.3 in the primary analysis of major congenital malformations, Cohort A will be compared to Cohort B1. In a secondary analysis of major congenital malformations, Cohort A will be compared to Cohort B overall and Cohort B2. All secondary outcome proportions in Cohort A will be compared to Cohort B, as well as separately with Cohorts B1 and B2 using the risk ratio (one-sided 97.5% CIs). The difference in proportions will also be compared to the defined clinical equivalence margin to reject the hypothesis that the rate in Cohort A is higher than in Cohort B1. Also, comparisons may be explored using risk ratios adjusted to relevant covariates through methods such as propensity score weighting, if the sample size is sufficient in subgroups of the covariates. The key covariates of interest that will be considered for adjustment are maternal age, prior history of elective or therapeutic pregnancy termination status, other

insomnia treatment exposures, and baseline alcohol, smoking, marijuana, and drug use. Other prior pregnancy and prior infant outcomes will be explored and considered for adjustment at the time of analysis.

The primary and secondary outcomes will be evaluated and described among subgroups of patients defined by key characteristics of interest including maternal age, race/ethnicity, smoking, and exposure to other insomnia medications [see Section 5.7.4.4].

External comparator cohort analysis

Prevalence for major congenital malformations in Cohort A will be assessed in parallel to the prevalence observed in available external comparator cohort(s) representing the background prevalence of birth defects in the general US and EEA population. The MACDP and EUROCAT classification of congenital malformations will be implemented to ensure comparability to US and EEA populations, respectively.

Categorical distributions available in the MACDP will be summarized using the same categories among the QUVIVIQ-exposed pregnancies. Indirect standardization methods will be applied for categorical distributions of maternal age, gestational age, and race/ethnicity. Indirect standardization involves calculating the observed number of events (i.e., major congenital malformations) and applying the maternal age, gestational age, and race/ethnicity distributions from the reference population (i.e., MACDP and EUROCAT) to calculate the expected number of major congenital malformations. The ratio of the observed number of major congenital malformations to the expected number of major congenital malformations is referred to as the standardized prevalence ratio.

Adjusted prevalence can be calculated by multiplying the standardized prevalence ratio by the crude congenital malformation rate.

It is important to emphasize that any external comparator data source and women enrolled in this study are 2 distinctly different datasets, thus “external adjustment methods” for inference comparisons are limited.

5.7.4.4 Sensitivity and subgroup analyses

Sensitivity analyses will be performed on both Cohort A and Cohort B if sufficient sample size allows, including but not limited to that which is listed in Table 6.

Table 6 Sensitivity analysis subgroups and outcomes analyzed

Subgroup	Outcome analyzed
Women who have received any prenatal testing that provides knowledge of pregnancy outcome, regardless of findings	Major congenital malformations
Women who have received any prenatal testing that provides knowledge of pregnancy outcome before enrollment, where results are known, regardless of the findings	Major congenital malformations
Women who received any first trimester prenatal screening that provides knowledge of pregnancy outcome before enrollment where result is known to be negative	Major congenital malformations
Women with exposure to QUVIVIQ preconception and in each trimester of exposure[a]	Major congenital malformations
Women with exposure to QUVIVIQ preconception and in each trimester of exposure	Minor congenital malformations
Women with exposure to insomnia medications (Cohorts A and B1) by type (continuous vs intermittent), duration, and dosage of exposure	Major congenital malformations
Women in the primary analysis	Spontaneous abortion occurring before 22 weeks of gestation
Women in primary analysis based on gestational age of enrollment	Spontaneous abortion
Women who did not take known teratogens during pregnancy	Major congenital malformations
Women with clinically confirmed insomnia disorder	Major congenital malformations
Women with exposure to QUVIVIQ and additional medications for insomnia treatment from preconception through end of pregnancy	Major congenital malformations

[a] The primary cut point will be the date of conception (LMP + 14 days) to the end of the first trimester (14 weeks gestation), additional sensitivity cut points will include 18 weeks prior to conception through the end of the first trimester, conception date to the end of the pregnancy, 18 weeks prior to conception to the end of pregnancy, second trimester exposure only, and third trimester exposure only.

LMP = last menstrual period.

Full details will be described in the SAP.

Subgroup analysis

Both Cohort A and Cohort B (overall and separately for Cohorts B1 and B2) will be summarized and compared for primary and secondary outcomes both overall and by the subgroups of the following parameters, if sufficient sample size allows:

- Maternal age category (< 18 years, 18 to < 35 years, 35 to 45 years, and 45 years and older).
- Race/ethnicity.
- Smoking status.
- Other classes of insomnia drugs used during pregnancy and/or during the infants first year of life (among live births).

Additional subgroups of interest may be explored beyond what is outlined above and will be detailed in the SAP.

Analysis of safety outcomes

Interim safety reporting will be conducted every year and will be aligned with the periodic benefit-risk evaluation report reporting schedule. All AE verbatim terms will be recorded and coded using MedDRA version 25.0 or later. All AEs and SAEs collected will be analyzed by preferred terms among prospective pregnancies (overall and within Cohort A, Cohort B1, Cohort B2) and among retrospective pregnancies where applicable.

External comparison

In addition to the internal comparison, results from prospective pregnancies will be descriptively compared to existing data sources or published reports representing the general population with prevalence of birth defects [see Section 5.4.4]. Additional external data sources will be considered if they become available during the study.

5.7.4.5 Case series analysis

Women with retrospective pregnancies who were exposed to QUVIVIQ during pregnancy or within 5 half-lives prior to conception will be included in a separate case series. Analyses in this case series will primarily be qualitative. Pregnancies included in this case series will be described with respect to demographic and clinical information [see Section 5.7.2.1] and QUVIVIQ exposure (e.g., timing of exposure and duration). All reported primary and secondary outcomes will be assessed in this analysis.

5.8 Quality control

5.8.1 Study documentation

The CC PI is responsible for maintaining adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, ICFs, and documentation of IRB and governmental notification.

5.8.2 Coordinating center audits and inspections

The CC inspections may be conducted by Idorsia or an authorized representative for the audit of study data, patients' medical records, and eCRFs.

The CC PI will also permit national and local health authorities to inspect facilities and records relevant to this study.

5.8.3 Retention of records

At the end of the study, the CC PI will receive the data related to patients from their CC in an electronically readable format. Data must be kept at the CC with the study documents. Acknowledgment of receipt of the data is required.

5.9 Limitations of the study methods

Although all possible measures will be taken to ensure the quality and robustness of the data, there are several limitations to the study design to be considered and acknowledged when interpreting the results of this study.

5.9.1 Internal validity of study design

5.9.1.1 Misclassifications

Assessing exposures: Recall of treatment and other potential exposures that could adversely impact the outcome of pregnancy is subject to variability based on the quality of collection by the HCP or the memory of the patient. Where applicable, calendars will be provided to aid the recall of past exposures.

Assessing the primary outcome: A committee of at least 3 qualified, independent teratologists or other appropriate birth defect experts will be used throughout the study to evaluate congenital malformations and other significant findings in Cohort A and Cohort B to ensure proper classification of the primary outcome [Section 10]. The Adjudication Committee will be blinded to QUVIVIQ exposure status to ensure that any misclassification remained after adjudication would be non-differential.

Misclassification of the primary and secondary outcomes remain possible, even with independent review. Where applicable, information provided by the HCP will override the information provided by the patient should there be a discrepancy.

5.9.1.2 Information bias

Patients with prospective pregnancies who have been informed about potential adverse pregnancy outcomes prior to enrollment in the study may exhibit differential recall of their treatment exposures during early pregnancy and may also stop their treatment after learning of the outcome. This study plans to enroll women whose fetal diagnosis has been made prior to enrollment in the registry (whether positive or negative) for major congenital malformations that are unrelated to genetic or aneuploid disorders, and women with or

without prenatal testing prior to enrollment that could determine the status of the fetus (e.g., amniocentesis, genetic testing, nuchal translucency screen, chorionic villus sampling, and late-term ultrasound). The differential recall may lead to bias, which will be addressed with the stratification of primary and secondary outcomes by the timing of enrollment with respect to the receipt of prenatal test results. Additionally, the primary analysis will exclude women who have received first trimester prenatal screening in which either aneuploid disorders or genetic disorders that are known to cause major congenital malformations have been detected.

Women with retrospective pregnancies may also have differential recall which may lead to bias and will not be compared to women with prospective pregnancies but will instead be analyzed in a separate case series.

Lastly, as the HCP is not blinded to the exposure status, HCPs may report AEs more frequently in patients exposed to QUVIVIQ than in patients unexposed to QUVIVIQ.

5.9.1.3 Selection bias

Spontaneous abortions most frequently occur in early pregnancy, likely before the pregnancy is recognized. Even if the pregnancy is recognized and confirmed, it is possible that the pregnancy may not be reported to the study if the loss occurred before enrollment in the study. Not capturing all early pregnancy losses will likely lead to an underestimation of the true early pregnancy loss rate. There is no reason to believe that this study will be differentially impacted by this bias, so even though the spontaneous early losses may be underestimated, the relative rate compared with the other registries should not be affected.

There is potential for channeling bias by label indication due to the severity of insomnia and patient insomnia treatment history. Women with more severe insomnia may be more likely to be prescribed QUVIVIQ compared to women with less severe insomnia histories. Baseline insomnia severity and prior treatments will be captured to assess the degree of confounding by indication.

5.9.1.4 Confounding

Covariates collected in both Cohort A and Cohort B include the following: pregnancy follow-up and frequency of mother and infant encounters, medical and medication history (including insomnia treatment), insomnia history, and pregnancy and infant outcomes. Careful selection of variables will be determined as confounding factors known to be associated with adverse pregnancy outcomes (e.g., maternal age, smoking, alcohol consumption, marijuana use, illicit drug use) to examine the distributions between Cohort A and Cohort B. The exploration of insomnia treatment exposures during pregnancy other than QUVIVIQ will also be performed by examining specific drugs and/or drug classes. Sensitivity analyses will complement existing primary analyses in controlling for confounding [see Section 5.7.4.4].

5.9.2 External validity of study design

To ensure internal comparability where feasible, Cohort B will be recruited from the same clinical centers through HCP awareness and use the same recruitment strategies [see Section 5.4.5] as Cohort A. However, the study population may not be reflective of the broader source population of pregnant women with insomnia. Participation in the study is completely voluntary which may lead to a particular type of patient group, such as women with severe insomnia who have taken medication(s) "at-risk" due to the severity of their condition. Additionally, there are a wide range of treatments for insomnia such that the distributions of insomnia treatment exposures in the study may not be reflective of the treatment distributions in the source population, which could impact generalizability.

As there are no patient-level data available for the external comparator cohorts, there may be underling differences between populations that are not detectable. However, reported categorical distributions of maternal age groups, race/ethnicity, or gestational age at birth may be available for comparison to ensure baseline similarities to the registry population and external adjustment methods (i.e., direct or indirect adjustment with a standard population) may be used.

5.9.3 Analytic limitations

Enrollment below the targeted sample size of 204 in Cohort A, 387 in Cohort B1, and 194 in Cohort B2 may limit the ability to address multiple strata or subgroups due to low sample size. The power of statistical comparisons to Cohort A of women with insomnia who are not exposed to QUVIVIQ could also be impacted by low enrollment; adjustment for covariates may not be feasible. The comparison of Cohort A to Cohort B will be performed and adjusted to relevant covariates if a sufficient number of outcomes are available. An interim analysis will be conducted at year 5 of the study to evaluate patient enrollment and inform awareness, recruitment, and retention plans as well as inform downstream sample size projections.

5.9.4 Limitations due to missing data and/or incomplete data

Reporting outcomes in this study is voluntary and it is possible that not all patients will complete all follow-up assessments. If data from a patient and their HCPs are unattainable, the patient will be considered lost to follow-up. It is possible that the outcomes from pregnancies lost to follow-up could differ from those with documented outcomes. Comparisons of characteristics of patients with completed information and those lost to follow-up will be conducted in an attempt to address this potential bias.

6 PROTECTION OF HUMAN SUBJECTS

The following steps will be taken to protect human subjects, data privacy, and other ethical considerations prior to enrollment into the study. Additional steps may be needed according to local regulation.

6.1 IEC/IRB approval

Approval from the IEC/IRB must be obtained before going through a consent procedure with the patient and before entering data into the database. The CC is covered under the registry's centralized IRB approach for registry reporting purposes.

6.2 Patient informed consent

Informed consent will be obtained for each study patient who self-enrolls or is enrolled by her HCP. Moreover, if required, the CC PI will obtain a signed Patient ICF from each patient (and/or legal guardian) whose data will be included in the project.

6.3 Patient confidentiality

The CC PI and research staff commit to complying with all related local laws and regulations. In the US, the regulations in 45 CFR parts 160 and 164 (protected health information), also known as the Health Insurance Portability and Accountability Act Privacy Regulations, will be followed. In EU countries, the EU Data Protection Act will be followed. If additional countries participate, patient confidentiality will be upheld according to the local regulations.

7 MANAGEMENT AND REPORTING OF ADVERSE EVENTS.

7.1 Definitions

7.1.1 Adverse event or adverse experience

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product irrespective of causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (e.g., including abnormal laboratory finding), symptom, or disease temporally associated with the use of a product, whether or not considered related to the product(s). The definition of an AE includes:

- Worsening of a pre-existing condition or underlying disease.
- Events associated with the discontinuation of the use of a product(s) (e.g., appearance of new symptoms).

It is the CC research staff's responsibility to document and communicate all AEs to Idorsia via a sponsor-approved method. The CC research staff or PI will not characterize reported events (e.g., seriousness, causality) but will serve as a conduit to Idorsia for appropriate follow-up and reporting.

7.1.2 Intensity of adverse events

Event severity is defined as a qualitative assessment of the degree of intensity as determined by the investigator or reported to him/her by the patient. The assessment of severity is made irrespective of intervention relationship or seriousness of the event and should be evaluated according to the following scale:

- Mild: The event is noticeable to the patient, but is easily tolerated, and does not interfere with the patient's daily activities.
- Moderate: The event is bothersome, possibly requiring additional therapy, and may interfere with the patient's daily activities.
- Severe: The event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the patient's daily activities.

Note: The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (as in mild, moderate, or severe pain); the event itself may be of relatively minor medical significance (such as severe headache). "Serious" is a regulatory definition and is based on patient or event outcome or action criteria usually associated with events that pose a threat to a patient's life or vital functions.

7.1.3 Serious adverse events

An SAE is any AE as defined above that meets at least 1 of the following serious criteria:

- Is fatal.
- Is life threatening (places the patient at immediate risk of death).
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is another "medically significant" event that does not meet any of the above criteria.

Obstetric complications that fall into the above categories are defined as SAEs in this study and should be reported to the CC research staff. Normal delivery and elective cesarean sections performed for non-medical reasons (i.e., scheduling, personal preference) and their related hospitalizations will not be considered SAEs, unless, in the opinion of the reporting physician, the hospitalization was prolonged due to a complication.

A hospitalization meeting the regulatory definition for "serious" is any in-patient hospital admission that includes a minimum of an overnight stay in a healthcare facility.

Other "medically significant" events refer to 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. Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

7.1.4 Relationship to the use of QUVIVIQ

For all events reported in patients exposed to QUVIVIQ, the treating physician or other reporting HCP will be asked to assess the relationship of the AE/SAEs to QUVIVIQ using the following definition: each AE/SAE must be assessed by the investigator/delegate as to whether or not there is a reasonable possibility of causal relationship to the study treatment and reported as either related or unrelated.

7.2 Adverse event / serious adverse event reporting

This study is collecting information from patients and HCPs from baseline/enrollment through the end of the study follow-up (i.e., in the event of patient loss to follow-up, withdrawn consent, death [mother and/or infant], pregnancy termination, study termination, or the end of study [whichever comes first]). All safety events considered to have occurred following patient exposure to QUVIVIQ will be collected during the observation period from the LMP through the end of study follow-up. HCPs will report maternal and fetal AEs and SAEs occurring during pregnancy and infant AEs or SAEs occurring during the infants' first year of life to the CC research staff, who will enter them into the eCRF. For patients exposed to QUVIVIQ, all pregnancies, positive pregnancy outcomes and adverse pregnancy outcomes (congenital malformations, spontaneous fetal losses, induced abortions), maternal events, and other relevant fetal events, regardless of attribution or seriousness, will be sent to Idorsia's Drug Safety Department within 1 business day or up to 3 calendar days of the CC's awareness. The CC research staff is responsible for ensuring that all safety events of which they become aware during the study period are recorded in the patient's appropriate study documentation.

7.3 Reporting of pregnancy

If a woman is exposed to QUVIVIQ during the follow-up period and reports a second pregnancy, this will be reported to Idorsia within 1 business day and the patient will be referred to join the pregnancy registry for a second time.

7.4 Reconciliation

Idorsia will perform a reconciliation of the registry database and Idorsia's drug safety database on a regular basis.

8 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Progress reports will be sent annually to the regulatory health authorities. A final study report will be submitted to the regulatory authorities, as applicable.

Publishing the results of the study in scientific literature should be done in adherence with Idorsia's Policies on Disclosure of Clinical Research Information and on Scientific Publications. Results should be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations of the research.

Publication of the study results should be submitted to a peer-reviewed journal and must be in accordance with the International Committee of Medical Journal Editors standards and the Strengthening the Reporting of Observational Studies in Epidemiology Statement [Von Elm 2007].

Authorship of any publications resulting from this study will be determined on the bases of the International Committee of Medical Journal Editors' Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals.

9 DATA OWNERSHIP

Idorsia is the data owner.

10 STUDY COMMITTEE

An Adjudication Committee of at least 3 qualified, independent individuals with expertise in obstetrics, embryology, teratology, pharmacology, epidemiology, pediatrics, clinical genetics, insomnia or other appropriate birth defect experts will be used throughout the study to evaluate congenital malformations and other significant findings. The Adjudication Committee will make recommendations on data collection and will assist in the review of data and classification of specific pregnancy outcomes. They will be blinded to the patient's exposure status to reduce any potential bias of outcome classification. Other experts in relevant specialties will also be consulted by Idorsia as deemed necessary by the external advisors.

11 REFERENCES

[ACOG 2017] American College of Obstetricians and Gynecologists (ACOG) Committee Opinion No. 700: Methods for Estimating the Due Date. Obstet Gynecol. 2017 May;129(5):e150-e154.

[ACOG 2018] American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin No. 190: gestational diabetes mellitus. Obstet Gynecol 2018;131(2):e49-e64.

[ACOG 2019] American College of Obstetricians and Gynecologists (ACOG). Preeclampsia and High Blood Pressure During Pregnancy: FAQ. April 2022 [accessed on 4 August 2022]. Available from: https://www.acog.org/womens-health/faqs/preeclampsia-and-high-blood-pressure-during-pregnancy

[Ancoli-Israel 2006] Ancoli-Israel S. The impact and prevalence of chronic insomnia and other sleep disturbances associated with chronic illness. Am J Manag Care 2006;12(8 Suppl):S221-9.

[Abalos 2013] Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. Eur J Obstet Gynecol Reprod Biol. 2013 Sep;170(1):1-7.

[Ammon Avalos 2012] Ammon Avalos L, Galindo C, Li DK. A systematic review to calculate background miscarriage rates using life table analysis. Birth Defects Research Part A: Clinical and Molecular Teratology. 2012 Jun;94(6):417-23.

[APA 2013] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. (DSM-5). Arlington, VA: American Psychiatric Publishing. 2013.

[Behboudi-Gandevani 2019] Behboudi-Gandevani S, Amiri M, Bidhendi Yarandi R, Ramezani Tehrani F. The impact of diagnostic criteria for gestational diabetes on its prevalence: a systematic review and meta-analysis. Diabetology & metabolic syndrome. 2019 Dec;11(1):1-8.

[CCSA 2022] Canadian Centre on Substance Use and Addition. Canadian Drug Summary: Setatives. May 2022. Available from: https://www.ccsa.ca/sites/default/files/2019-06/CCSA-Canadian-Drug-Summary-Sedatives-2019-en.pdf

[Calderon-Margalit 2009] Calderon-Margalit R, Qiu C, Ornoy A, Siscovick DS, Williams MA. Risk of preterm delivery and other adverse perinatal outcomes in relation to maternal use of psychotropic medications during pregnancy. American journal of obstetrics and gynecology. 2009 Dec 1;201(6):579-e1.

[CDC 2008] Centers for Disease Control and Prevention. Update on overall prevalence of major birth defects – Atlanta, Georgia, 1978-2005. 11 January 2008 [accessed on 12 April 2023]. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5701a2.htm

[CDC 2019] Centers for Disease Control and Prevention (CDC). Developmental Milestones. CDC's Developmental Milestones. 29 December 2022 [accessed on 12 April 2023]. Available from: https://www.cdc.gov/ncbddd/actearly/milestones/index.html

[CDC 2021] Centers for Disease Control and Prevention (CDC). Metropolitan Atlanta Congenital Defects Program (MACDP). 16 March 2022 [accessed 12 April 2023]. Available from: https://www.cdc.gov/ncbddd/birthdefects/macdp.html

[cdc.gov_a] Centers for Disease Control and Prevention [Internet]. U.S. Department of Health & Human Services [cited 19 August 2022] Preterm Birth. Available from: https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pretermbirth.htm

[cdc.gov_b] Centers for Disease Control and Prevention [Internet]. U.S. Department of Health & Human Services [cited 19 August 2022] Low Birth Rate. Available from: https://www.cdc.gov/nchs/fastats/birthweight.htm

[Chang 2010] Chang JJ, Pien GW, Duntley SP, Macones GA. Sleep deprivation during pregnancy and maternal and fetal outcomes: is there a relationship? Sleep Med Rev 2010;14(2):107-14.

[Chimah 2022] Chimah OU, Emeagui KN, Ajaegbu OC, Anazor CV, Ossai CA, Fagbemi AJ, et al. Congenital malformations: Prevalence and characteristics of newborns admitted into Federal Medical Center, Asaba. Health Science Reports. 2022 May;5(3):e599.

[Clifford 1974] Clifford JM, Cookson JH, Wickham PE. Absorption and clearance of secobarbital, heptabarbital, methaqualone, and ethinamate. Clinical Pharmacology & Therapeutics. 1974 Aug;16(2):376-89.

[Correa 2007] Correa A, Cragan JD, Kucik JE, Alverson CJ, Gilboa SM, Balakrishnan R, et al. Reporting birth defects surveillance data 1968-2003. Birth Defects Res A Clin Mol Teratol 2007;79(2):65-186.

[Danforth 2008] Danforth DN. Danforth's obstetrics and gynecology. 10th ed. Lippincott Williams & Wilkins; 2008.

[Duke 2014] Duke W, Gilboa SM. Using an existing birth defects surveillance program to enhance surveillance data on stillbirths. J Registry Manag 2014;41(1):13-8.

[EMA 2005] European Medicines Agency. Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-Authorisation Data. EMEA/CHMP/313666/2005. 14 November 2005 [accessed 12 April 2023]. Available from: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-exposure-medicinal-products-during-pregnancy-need-post-authorisation-data_en.pdf

[EC 2022] European Commission. EUROCAT data: Prevalence charts and tables. 20 December 2022 [accessed 12 April 2023]. Available from: https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence_en

[FDA 2002] US Food and Drug Administration. Guidance for Industry: Establishing Pregnancy Exposure Registries. August 2022 [accessed 14 March 2023]. Available from: https://www.fda.gov/media/75607/download#:~:text=V.-,WHEN%20SHOULD%20SUCH%20A%20REGISTRY%20BE%20ESTABLISHED%3F,of%20successfully%20completing%20the%20registry.

[FDA 2019a] US Food and Drug Administration. Guidance for Industry: Postapproval Pregnancy Safety Studies, Draft Guidance. May 2019 [accessed 12 April 2023]. Available from: https://www.fda.gov/media/124746/download

[FDA 2019b] US Food and Drug Administration. Sleep Disorder (Sedative-Hypnotic) Drug Information. 30 April 2019 [accessed 14 March 2023]. Available from: https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/sleep-disorder-sedative-hypnotic-drug-information

[FDA 2022] US Food and Drug Administration. Drug Approvals and Databases. 8 August 2022 [accessed 14 March 2023]. Available from: https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases

[Fenton 2013] Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr 2013;13:59.

[Gliklich 2014] Gliklich RE, Dreyer NA, Leavy MB, editors. Registries for evaluating patient outcomes: a user's guide [Internet]. 3rd ed. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014. Report No.: 13(14)-EHC111.

[go.drugbank.com] DrugBank Online [Internet]. [cited 14 March 2023]. Available from: https://go.drugbank.com/

[Groen 2017] Groen H, Bouman K, Pierini A, Rankin J, Rissmann A, Haeusler M, et al. Stillbirth and neonatal mortality in pregnancies complicated by major congenital anomalies: findings from a large European Cohort. Prenat Diagn 2017;37(11):1100-11.

[HMA 2017] Heads of Medicines Agency. European Medicines Agency Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-authorisation safety studies (Rev 3). 9 October 2017 [accessed on 13 April 2023]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-viii-post-authorisation-safety-studies-rev-3_en.pdf

[Hug 2021] Hug L, You D, Blencowe H, Mishra A, Wang Z, Fix MJ, et al. Global, regional, and national estimates and trends in stillbirths from 2000 to 2019: a systematic assessment. The Lancet. 2021 Aug 28;398(10302):772-85.

[Huitfeldt 2020] Huitfeldt A, Sundbakk LM, Skurtveit S, Handal M, Nordeng H. Associations of maternal use of benzodiazepines or benzodiazepine-like hypnotics during pregnancy with immediate pregnancy outcomes in Norway. JAMA Network Open. 2020 Jun 1;3(6):e205860-.

[ISPE 2008] International Society of Pharmacoepidemiology. Guidelines for good pharmacoepidemiology practices (GPP). Pharmacoepidemiol Drug Saf 2008;17(2):200-8.

[Jones 2017] Jones RK, Jerman J. Abortion incidence and service availability in the United States, 2014. Perspectives on sexual and reproductive health. 2017 Mar;49(1):17-27.

[Jostell 1978] Jostell KG, Agurell S, Allgén LG, Kuylenstierna B, Lindgren JE, Åberg G, et al. Pharmacokinetics of clomethiazole in healthy adults. Acta pharmacologica et toxicologica. 1978 Sep;43(3):180-9.

[Kwok 2017] Kwok KK, Vincent EC, Gibson JN. 36 – Antineoplastic Drugs. In: Pharmacology and Therapeutics for Dentistry. 7th ed. Maryland Heights: Mosby; 2017:530-562.

[Lewis 2010] Levis MJ. Will newer tyrosine kinase inhibitors have an impact in AML? Best Pract Res Clin Haematol. 2010 Dec;23(4):489-94.

[Lie 2015] Lie J, Tu K, Shen D, Wong B. Pharmacological Treatment of Insomnia. P T 2015;40(11):759-71.

[Lupattelli 2019] Lupattelli A, Chambers CD, Bandoli G, Handal M, Skurtveit S, Nordeng H. Association of Maternal Use of Benzodiazepines and Z-Hypnotics During Pregnancy with Motor and Communication Skills and Attention-Deficit/Hyperactivity Disorder Symptoms in Preschoolers. JAMA Netw Open. 2019 Apr 5;2(4):e191435.

[Machin 1987] Machin DE, Campbell MJ. Statistical tables for the design of clinical trials. Blackwell Mosby Book Distributors. 1987.

[May 1994] May TW, Korn-Merker E, Rambeck B, Boenigk HE. Pharmacokinetics of sulthiame in epileptic patients. Ther Drug Monit. 1994 Jun;16(3):251-7.

[McLaughin 2022] McLaughlin JM, Khan F, Schmitt HJ, Agosti Y, Jodar L, Simões EA, et al. Respiratory Syncytial Virus–Associated Hospitalization Rates among US Infants: A Systematic Review and Meta-Analysis. The Journal of infectious diseases. 2022 Mar 15;225(6):1100-11.

[medicines.org.uk] medicines.org.uk [Internet] Electronic Medicines Compendium (EMC). [cited 14 March 2023]. Available from: http://medicines.org.uk/emc/

[Mignot 2022] Mignot E, Mayleben D, Fietze I, Leger D, Zammit G, Bassetti CLA, et al. Investigators. Safety and efficacy of daridorexant in patients with insomnia disorder: results from two multicentre, randomised, double-blind, placebo-controlled, phase 3 trials. Lancet Neurol. 2022 Feb;21(2):125-139.

[Mind.org] Mind.org [Internet]. Sleeping pills & Minor Tranquillisers A-Z. April 2021 [cited 14 March 2023]. Available from: https://www.mind.org.uk/information-support/drugs-and-treatments/sleeping-pills-and-minor-tranquillisers-a-z/overview/

[Nodine 2013] Nodine P, Matthews E. Common sleep disorders: management strategies and pregnancy outcomes. J Midwifery Womens Health 2013;58(4): 368-77.

[Osterman 2023] Osterman M, Hamilton B, Martin J, Driscoll A, Valenzuela C. Births: Final data for 2021. National Vital Statistics Reports. 2023; 72(1).

[Polifka 2002] Polifka JE, Friedman JM. Medical genetics: 1. Clinical teratology in the age of genomics. CMAJ 2002;167(3):265-73.

[products.mhra.gov.uk] products.mhra.gov.uk [Internet] Medicines & Healthcare Products Regulatory Agency. [cited 14 March 2023]. Available from: https://products.mhra.gov.uk/

[Ratliff 1998] Ratliff AF, Wilson J, Hum M, Marling-Cason M, Rose K, Winick N, et al. Phase I and pharmacokinetic trial of aminopterin in patients with refractory malignancies. J Clin Oncol. 1998 Apr;16(4):1458-64.

[Reed 2013] Reed CE, Fenton SE. Exposure to diethylstilbestrol during sensitive life stages: a legacy of heritable health effects. Birth Defects Res C Embryo Today. 2013 Jun;99(2):134-46.

[Reichner 2015] Reichner CA. Insomnia and sleep deficiency in pregnancy. Obstet Med 2015;8(4):168-71.

[Schwartsmann 1998] Schwartsmann G, van der Vijgh WJ, van Hennik MB, Klein I, Vermorken JB, Dodion P, et al. Pharmacokinetics of Brequinar sodium (NSC 368390) in patients with solid tumors during a phase I study. Eur J Cancer Clin Oncol. 1989 Dec;25(12):1675-81.

[Sclaudecker 2017] Schlaudecker EP, Munoz FM, Bardají A, Boghossian NS, Khalil A, Mousa H, et al. Small for gestational age: Case definition & guidelines for data collection, analysis, and presentation of maternal immunisation safety data. Vaccine. 2017 Dec 12;35(48Part A):6518.

[Sivertsen 2021] Sivertsen B, Pallesen S, Friborg O, Nilsen KB, Bakke OK, Goll JB, et al. Sleep patterns and insomnia in a large population-based study of middle-aged and older adults: The Tromso study 2015-2016. J Sleep Res 2021;30(1):e13095.

[TGA 2011] Therapeutic Goods Administration (TGA) Australian Department of Health and Aged Care. Australian categorisation system for prescribing medicines in pregnancy. 4 May 2011 [accessed on 12 April 2023]. Available from: https://www.tga.gov.au/australian-categorisation-system-prescribing-medicines-pregnancy

[TGA 2019]. Therapeutic Goods Administration (TGA) Australian Department of Health and Aged Care. Prescribing medicines in pregnancy database. November 2019 [accessed on 12 April 2023]. Available from: https://www.tga.gov.au/prescribing-medicines-pregnancy-database

[Thorpy 2012] Thorpy MJ. Classification of sleep disorders. Neurotherapeutics 2012;9(4):687-701.

[Turner 2017] Turner K, Hameed AB. Hypertensive disorders in pregnancy current practice review. Current Hypertension Reviews. 2017 Aug 1;13(2):80-8.

[Valla 2015] Valla L, Wentzel-Larsen T, Hofoss D, Slinning K. Prevalence of suspected developmental delays in early infancy: results from a regional population-based longitudinal study. BMC pediatrics. 2015 Dec;15(1):1-8.

[Ventura 2000] Ventura SJ, Mosher WD, Curtin SC, Abma JC, Henshaw S. Trends in pregnancies and pregnancy rates by outcome: estimates for the United States, 1976-96. Vital and health statistics. Series 21, Data on natality, marriage, and divorce. 2000 Jan 1(56):1-47.

[Von Elm 2007] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ 2007;335:806-8.

[Wang 2010] Wang LH, Lin HC, Lin CC, Chen YH, Lin HC. Increased risk of adverse pregnancy outcomes in women receiving zolpidem during pregnancy. Clinical Pharmacology & Therapeutics. 2010 Sep;88(3):369-74.

[Walani 2020] Walani SR. Global burden of preterm birth. International Journal of Gynecology & Obstetrics. 2020 Jul;150(1):31-3.

[WHO 1995] World Health Organization. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. World Health Organ Tech Rep Ser. 1995. [accessed on 12 April 2023]. Available from: https://apps.who.int/iris/bitstream/handle/10665/37003/WHO_TRS_854.pdf?sequence=1&isAllowed=y

[who.int] World Health Organization. [Internet] Infant Mortality; c2023 [cited 12 April 2023]. Global Health Observatory. Available from: https://www.who.int/data/gho/data/themes/topics/indicator-groups/indicator-group-details/GHO/infant-mortality#:~:text=Globally%2C%20the%20infant%20mortality%20rate,to%204.0%20million%20in%202018

12 APPENDICES

Appendix 1 Data collection overview for prospective pregnancies (as per standard-of-care)

	Enrollment	**Prenatal Follow-up**			**Pregnancy Outcome**	**Pediatric Follow-Up**	**Early Termination Visit**
Data Collection [a]		**End First Trimester (~14 weeks)**	**Mid-Second Trimester (~21 weeks)**	**Mid-Third Trimester (~34 weeks)**	**~4 Weeks After Estimated Delivery Date**	**Infant aged 12, 26, and 52 weeks**	**End of Patient Participation in Study**
Informed consent [b]	X						
Reporter of information [c]	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X						
Patient demographics and characteristics [d]	X	X	X	X			
Medical history [e]	X						
Pregnancy history, and current pregnancy information [f]	X						
Lifestyle factors [g]	X	X	X	X	X		
Prior and concomitant medications, including other insomnia treatment [h]	X	X	X	X	X		X
QUVIVIQ prescription information [i]	X	X	X	X	X		X
Comorbid conditions	X	X	X	X	X		
Insomnia history and treatment status [j]	X	X	X	X	X		
Current pregnancy status		X	X	X	X		X [k]
Gestational age (weeks)	X	X	X	X	X		X [k]
Pregnancy outcome [l]		X	X	X	X		X [k]
Infant characteristics					X [m]	X [n]	X [k]
Infant abnormalities [o]					X	X	X [k]

	Enrollment	Prenatal Follow-up			Pregnancy Outcome	Pediatric Follow-Up	Early Termination Visit
Data Collection [a]		**End First Trimester (~14 weeks)**	**Mid-Second Trimester (~21 weeks)**	**Mid-Third Trimester (~34 weeks)**	**~4 Weeks After Estimated Delivery Date**	**Infant aged 12, 26, and 52 weeks**	**End of Patient Participation in Study**
Medication use of nursing mother						X	
Patient/infant AEs and SAEs [p]	X →						
Reason for early termination							X

[a] Available data will be collected; no additional diagnostic or monitoring procedures shall be applied to the patients outside of routine clinical practice.
[b] Written or electronic informed consent must be obtained before any data collection (per local regulations or IRB requirements).
[c] Including the patient or HCP (e.g., primary care provider, obstetrician, insomnia specialist, psychiatrist, nurse midwife, infant HCP, other).
[d] Including age of mother, education level, race/ethnicity, height, and pre-pregnancy and current pregnancy weight.
[e] Including surgical and medical history/significant maternal medical conditions other than insomnia, insomnia history, family reproductive history.
[f] Including previous pregnancy outcomes, detailed family history including pregnancy complications, adverse pregnancy outcomes and developmental abnormalities, and information about baseline risks.
[g] Including smoking, use of caffeine, use of alcohol, and use of recreational drugs before and during current pregnancy.
[h] Current and prior medication use starting from 3 months prior to conception (including all other prescription and OTC insomnia treatments, folic acid, vitamins, herbal remedies or supplements, vaccinations, or other medications used to treat chronic conditions or comorbidities).
[i] Start and stop dates, dose, dosing frequencies, reason for discontinuation (if applicable).
[j] Insomnia and insomnia treatment status since last follow-up.
[k] If applicable.
[l] Including live births, spontaneous abortions, stillbirths, elective or therapeutic terminations, reason for elective or therapeutic termination (e.g., prenatal testing findings, risk to mother's health, undesired pregnancy), mode of birth, and autopsy results and pathology results, if applicable.
[m] Gestational age, sex, weight, length, head circumference, birth order (for multiple births), Apgar scores, breastfeeding status, vaccine information, and evidence of any abnormality, if applicable.
[n] Including postnatal growth and development, feeding behavior, weight, length, head circumference, breastfeeding status, vaccination information, and evidence of any abnormality, if applicable.
[o] Detailed information on any infant abnormalities identified after infant birth.
[p] Patient or infant AEs and SAEs in Cohort A and Cohort B during the observation period from the LMP through the end of study follow-up (including event, start date, ongoing or end date, seriousness, severity, relationship to QUVIVIQ, outcome, action take). HCPs will report maternal and fetal AEs and SAEs occurring during pregnancy and infant AEs and SAEs during the infant's first year of life, where applicable to the CC.
AE = adverse event; CC = coordinating center; HCP = healthcare provider; IRB = Institutional Review Board; LMP = last menstrual period; OTC = over-the-counter; SAE = serious adverse event.

Appendix 2 List of known teratogens

This list of known teratogens and their half-lives (last updated 1 March 2023) will be used for exclusion purposes in the analysis. This list will be reviewed at the time of analysis to update it with any changes since protocol finalization.

Substance	**Half-Life**
Acitretin	49 hours
Acenocoumarol	8–11 hours
Afatinib	37 hours
Aflibercept	5–6 days
Alitretinoin	9 hours
Altretamine	4.7–10.2 hours
Azacitidine	41 minutes
Arsenic trioxide	10–14 hours
Ambrisentan	9 hours
Aminopterin[a]	3.6 hours
Amsacrine	8–9 hours
Asparaginase	14.2–44.2 hours
Axitinib	2.5–6.1 hours
Azathioprine	5 hours
Benazepril	10–11 hours
Bendamustine	28.2 minutes
Bevacizumab	18 days
Bexarotene	1–3 hours
Bleomycin	115 minutes
Bortezomib	40–193 hours
Bosutinib	36 hours
Brequinar[b]	11.1–36.6 minutes in initial phase, 12.5–25.0 hours in terminal phase
Busulfan	2.3–2.5 hours
Bosentan	5 hours
Cabazitaxel	95 hours
Cabozantinib	110 hours
Capecitabine	0.8–0.9 hours
Carboplatin	90 minutes–6 hours
Carmustine	96 hours
Cetuximab	70–100 hours

Substance	**Half-Life**
Chlorambucil	1.8 h
Chlortetracycline	5.6 h
Cisplatin	25–49 min
Cladribine	1 day
Clofarabine	5.2 h
Ceritinib	31–41 h
Clomiphene	5–7 days
Clorazepate	2 days
Cytarabine	10 min
Captopril	< 3 h
Carbamazepine	35 h
Cyclophosphamide	3–12 h
Danazol	9–23.7 h
Demeclocycline	10–16 h
Doxycycline	18–22 h
Dutasteride	5 weeks
Dabrafenib	10 h
Dacarbazine	2.9–75 min
Dactinomycin	36 h
Dasatinib	5-6 h
Daunorubicin	45 min in initial phase, 18.5 h in terminal phase
Didanosine	30 min
Diethylstilbestrol[c]	2–3 days
Divalproex	13–19 h
Docetaxel	4 min–11 h pending phase
Dolutegravir	14 h
Doxorubicin	12 min–30 h pending phase
Enalapril	14 h
Enalaprilat	11 h
Enzalutamide	5.8 days
Ethosuximide	17–56 h
Epirubicin	40 h
Erlotinib	36.2 h
Estramustine	20 h
Ethotoin	3–9 h

Substance	**Half-Life**
Etoposide	0.6–2 h
Etretinate	49 h
Eribulin	40 h
Everolimus	30 h
Finasteride	4.5 h
Fluconazole (chronic, high-dose only)	20–50 h
Fosinopril sodium	12 h
Fosphenytoin sodium	15 min
Fenprocoumon	5–6 days
Floxuridine[e]	10–20 min
Fluorouracil	10–20 min
Gefitinib	48 h
Gemcitabine	19.4 h
Hydroxycarbamide	12 h
Hydroxyurea	12 h
Ibrutinib	4–6 h
Idarubicin	15 h
Ifosfamide	15 h
Imatinib	18 – 40 h
Isotretinoin	18 h
I-131	8 days
Irinotecan	6–12 h
Ixabepilone	52 h
Kanamycin	2.5 h
Ledipasvir/sofosbuvir with ribavirin	ribavirin 12 days
Leflunomide	2 weeks
Lenalidomide	13 h
Lisinopril	12 h
Lisinopril + hydrochlorothiazide	13 h
Lapatinib	6–14 h
Lenvatinib	28 h
Lestaurtinib[f]	8–12 h
Lomustine	6 h
Macitentan	14.1–18.5 h
Matinib	18–40 h
Methimazole	4.9–5.7 h

Substance	**Half-Life**
Methotrexate	lower doses: 3–10 h higher doses: 8–15 h
Methylene blue	24 h
Minocycline	11–24.31 h
Misoprostol	20–40 min
Moexipril	1.3 h
Mechlorethamine	15 min
Melphalan	10–75 min
Mercaptopurine	90 min
Mesterolone	12–13 h
Methacycline	14 h
Methsuximide	1.4–2.6 h for mesuximide, 28–38 h for the active metabolite
Methylfenobarbital	11–67 h
Methyltestosterone	6–8 h
Mitomycin	8–48 min
Mitoxantrone	75 h
Mycophenolate mofetil	18 h
Mycophenolic acid	8–16 h
Nandrolone	6 days
Nelarabine	30 min – 3 h
Nilotinib	17 h
Nintedanib	10–15 h
Oxaliplatin	0.43–16.8 h
Oxandrolone	0.55 h
Oxcarbazepine	1.3–2.3 h
Oxytetracycline	6–8 h
Paritaprevir/ritonavir/ombitasvir/dasabuvir/ribavirin	ribavirin 12 days
Penicillamine	1–7.5 h
Phenytoin	12–28.9 h
Perindopril	30–120 h
Pomalidomide	9.5 h
Primidone	7–22 h
Propylthiouracil	24 h
Paclitaxel	3.0–52.7 h
Paroxetine	1 day
Pasterone	12 h

Substance	**Half-Life**
Pemetrexed	3.5 h
Procarbazine	10 min
Pentostatin	2.6–16 h
Phenobarbital	90–100 h
Quinapril	25 h
Radium (223Ra) dichloride	11.4 days
Raloxifene	32.5 h
Ramipril	13–17 h
Raltitrexed	198 h
Ribavirin	12 days
Riociguat	10 h
Simeprevir with ribavirin and peginterferon alfa	ribavirin 12 days
Sofosbuvir/velpatasvir with ribavirin	ribavirin 12 days
Sofosbuvir with peginterferon alfa and ribavirin	ribavirin 12 days
Sofosbuvir with ribavirin	ribavirin 12 days
Streptomycin	5–6 h
Sorafenib	25–48 h
Streptozocine	5–15 min
Sultiam[g]	8.7 h
Sunitinib	40–60 h
Tetracycline	8–10 h
Teriflunomide	19 days
Thalidomide	5–7 h
Topiramate	21 h
Trandolapril	6 h
Tretinoin (oral)	0.5–2 h
Trimethoprim	8–10 h
Tazotarotene	18 h
Tegafur	11 h
Telavancin	8 h
Temozolomide	1.8 h
Teniposide	5 h
Testosterone	1–100 min
Thioguanine	25-240 min
Thiotepa	1.5–4.1 h
Tigecycline	27–43 h

Substance	Half-Life
Topotecan	2–3 h
Trimethadione/paramethadione	12–24 (paramethadione)
Trimetrexate glucoronate	11–20 h
Valproate sodium	16 h
Valproic acid	9–16 h
Vismodegib	12 days (single-dose) 4 days (continuous use)
Vigabatrin	5–8 h
Vinblastine	Initial: 35 min Middle: 53 h Terminal: 19 h
Vincristine	Initial: 5 min Middle: 2.3 h Terminal: 85 h
Vindesine	24 h
Vinorelbine	27.7–43.6 h
Vitamin A	1.9 h
Warfarin (coumadin)	1 week

Note: Unless otherwise noted, this list was generated using the Australian Department of Health TGA prescribing medicines in pregnancy database [TGA 2011; TGA 2019], Medicines.org.uk [medicines.org.uk], Accessdata.fda.gov [FDA 2002] , and the DrugBank Online database [go.drugbank.com]. Product information was adapted based on availability in the US market (removing drugs not available in the US and adding teratogens available in the US but not Australia). Lastly, the list was then cross-referenced against Polifka and Friedman [Polifka 2002] for any FDA-approved prescribing medicines that are designated as known teratogens.

[a]Source data: [Ratliff 1998]
[b]Source data: [Schwartsmann 1998]
[c]Source data: [Reed 2013]
[d]Source data: [Kwok 2017]
[f]Source data: [Lewis 2010]
[g]Source data: [May 1994]

FDA = Food and Drug Administration; TGA = Therapeutic Goods Administration; US = United States.

Appendix 3 List of approved non-ORA medications to treat insomnia

This list of known, approved non-ORA medications to treat insomnia or sleep disorders is based the information as of 26 June 2023. This list will be reviewed at the time of analysis to update it with any changes since protocol finalization.

Medication name	**Half-life[a]**	**Medication availability**	**Known teratogen**
Alprazolam	10.7–15.8 h	Prescription	No
Amobarbital	16-40 h	Prescription	No
Butabarbital	100 h	Prescription	No
Brotizolam	14.9 min	Prescription	No
Buspirone	2–3 h	Prescription	No
Chloral hydrate	4–12 h	Prescription	No
Chlordiazepoxide	6–30 h	Prescription	No
Cinolazepam	9 h	Prescription	No
Clomethiazole[b]	3.5–5 h	Prescription	No
Cloral betanine	4–12 h	Prescription	No
Diazepam	48 h	Prescription	No
Diphenhydramine	2.4–9.3 h	Over-the-counter	No
Doxepin	15.3 h	Prescription	No
Doxylamine	10 h	Over-the-counter	No
Estazolam	10–24 h	Prescription	No
Eszopiclone	6 h	Prescription	No
Etizolam	3.4–6 h	Prescription	No
Flunitrazepam	72 h	Prescription	No
Flurazepam	3.1 h	Prescription	No
Loprazolam	12 h	Prescription	No
Lorazepam	14 h	Prescription	No
Lormetazepam	13.6 h	Prescription	No
Melatonin	45 min	Over-the-counter	No
Nitrazepam	24 h	Prescription	No
Oxazepam	6–20 h	Prescription	No
Pentobarbital	15-50 h	Prescription	No
Phenobarbital	53–118 h	Prescription	No
Pregabalin	6.3 h	Prescription	No
Promethazine	9–16 h	Prescription	No
Quazepam	30 min	Prescription	No
Ramelteon	2.6 h	Prescription	No

Medication name	Half-life[a]	Medication availability	Known teratogen
Ramelteon	1–2.6 h	Prescription	No
Secobarbital[c]	28.9 h	Prescription	No
Tasimelteon	1.3 h	Prescription	No
Triazolam	0.4–18.4 h	Prescription	No
Temazepam	1.5–5.5 h	Prescription	No
Zaleplon	1 h	Prescription	No
Zolpidem	2.5–2.6 h	Prescription	No
Zopiclone	6 h	Prescription	No

Note: This list was generated from the US FDA list of known sleep disorder medications [FDA 2019b], the UK list of sleeping pills and minor tranquilizers [Mind.org], the DrugBank Online database [go.drugbank.com], and the Canadian Drug Summary: Sedatives list [CCSA 2022]. The list was then crosschecked for known teratogenicity against the teratogens provided in Appendix 2. Medications withdrawn at time of protocol approval: Butabarbital and Estazolam

[a] Unless otherwise noted, product half-life was extracted from Accessdata.fda.gov [FDA 2022], https://products.mhra.gov.uk/ [products.mhra.gov.uk], and the DrugBank Online database [go.drugbank.com].

[b] Source data: [Jostell 1978].

[c] Source data: [Clifford 1974].

FDA = Food and Drug Administration; UK = United Kingdom; US = United States.

Appendix 4 List of exposure windows for secondary outcomes

As detailed in the FDA's *Postapproval Pregnancy Safety Studies, Guidance for Industry Section B.10* [FDA 2019a], separate analyses will be performed for each pregnancy outcome. The primary analysis for major congenital malformations will be based on exposure to QUVIVIQ within 5 half-lives prior to conception or the first trimester [see Sections 5.7.1.3 and 5.7.4.4]. For the secondary outcomes, subgroup analyses based on the timing of exposure (preconception, first trimester, second trimester, third trimester) will be conducted as sample size permits. Consistent with prior research on sleep medications in pregnancy [Huitfeldt 2020, Lupattelli 2019, Calderon-Margalit 2009, Wang 2010], each outcome will be assessed with respect to exposure timing as outlined in this table.

Secondary outcome of interest	**Exposure timing for evaluation in analyses**
Pregnancy complications	
Preeclampsia	Preconception, first trimester, second trimester, third trimester
Pregnancy-induced hypertension	Preconception, first trimester, second trimester, third trimester
Preterm labor	Preconception, first trimester, second trimester, third trimester
Gestational diabetes	Preconception, first trimester, second trimester, third trimester
Pregnancy outcomes	
Elective and therapeutic abortion	Preconception, first trimester, second trimester, third trimester
Spontaneous abortion	Preconception, first trimester, second trimester
Fetal death or stillbirth	Preconception, first trimester, second trimester, third trimester
Live birth	Preconception, first trimester, second trimester, third trimester
Preterm birth	Preconception, first trimester, second trimester, third trimester

Infant outcomes	
Minor congenital malformations	Preconception, first trimester, second trimester, third trimester
Size for gestational age	Preconception, first trimester, second trimester, third trimester
Infant death	Preconception, first trimester, second trimester, third trimester
Hospitalization for serious illness	Preconception, first trimester, second trimester, third trimester
Postnatal growth and development	Preconception, first trimester, second trimester, third trimester

Preconception: within 5 half-lives prior to conception (LMP + 14 days), First trimester: conception to 13^{+6} weeks' gestation, Second trimester: 14^{+0} to 27^{+6} weeks' gestation, Third trimester: 28^{+0} weeks' gestation to end of pregnancy.