Redacted Protocol I8F-MC-B016
Tirzepatide Pregnancy Registry:

A Multi-Country Registry-Based Observational Study to Assess Maternal, Fetal, and Infant Outcomes Following Treatment with Tirzepatide for Weight Management During Pregnancy

Protocol Electronically Signed and Approved by Lilly: approval date provided below

Document ID: VV-PVG-114238

Approved on 16 Oct 2025 GMT

Post-Authorization Safety Study (PASS) Information

Title	Tirzepatide Pregnancy Registry: A Multi-Country Registry-Based Observational Study to Assess Maternal, Fetal, and Infant Outcomes Following Treatment with Tirzepatide for Weight Management During Pregnancy
Study Identifier	I8F-MC-B016 (2024-13280)
Version Identifier	V5.0
HMA-EMA Catalogues of real-world data sources and studies register number:	EUPAS1000000517
Active Substance	Glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist, A10BX16, Tirzepatide
Medicinal Product(s)	Zepbound® (Mounjaro® in some countries outside of the US)
Product Reference	LY3298176
Procedure Number	Not applicable
Marketing Authorization Holder(s)	Eli Lilly and Company
Joint PASS	Not applicable

Research Question and Objectives	The aim of the Tirzepatide Pregnancy Registry study is to compare the maternal, fetal, and infant outcomes of individuals treated with tirzepatide for weight management during pregnancy (tirzepatide exposed cohort) with outcomes in two comparator cohorts: • Anti-obesity medication [AOM] active comparator cohort: Individuals who are treated with pharmacotherapy other than tirzepatide or other therapies with GLP-1 receptor agonist (GLP-1 RA) activity for weight management during pregnancy • AOM unexposed comparator cohort: Individuals who have obesity or are overweight with at least one weight-related comorbid condition at the time of conception; and who are not treated with tirzepatide, GLP-1 RA therapies, or any products for weight management during pregnancy The primary objective is to describe and compare the overall prevalence of major congenital malformations (MCM) among individuals treated with tirzepatide for weight management during pregnancy relative to the two comparator cohorts of pregnant individuals (AOM active comparator cohort and AOM unexposed comparator cohort). The secondary objective is to describe and compare the prevalence of maternal pregnancy complications, fetal and infant outcomes other than MCM, and postnatal growth and development outcomes between pregnant individuals treated with tirzepatide for weight management during pregnancy and the two comparator cohorts of pregnant individuals (AOM active comparator cohort and AOM unexposed comparator cohort). The secondary outcomes of interest are as follows: Maternal pregnancy complications • Gestational diabetes • Pregnancy-induced hypertension • Pre-eclampsia • Eclampsia Fetal outcomes • Spontaneous abortion (SAB) • Induced abortion • Stillbirth Infant outcomes • Minor congenital malformations • Preterm birth • Small for gestational age (SGA) Postnatal growth and development outcomes • Postnatal growth deficiency (up to one year of age) • Infant developmental delay (up to one year of age)
Country(ies) of study	United States, United Kingdom, and Germany

Authors	Sponsor - Eli Lilly and Company Vendor - PPD®, part of Thermo Fisher Scientific®

Abbreviations: PAS = Post-Authorization Study; PASS = Post-Authorization Safety Study.

Marketing Authorization Holder

Marketing Authorization Holder (MAH)	Eli Lilly and Company
MAH Contact Person	Lilly Global Patient Safety Pharmacoepidemiologist

1. Table of Contents

Section **Page**

List of Tables

Table **Page**

List of Figures

Figure **Page**

List of Annexes

2. List of Abbreviations

Term	Definition
ACOG	American College of Obstetricians and Gynecologists
AE	Adverse event
AOM	Anti-obesity medication
ART	Assisted reproductive technology
AUC	Area under the curve
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
eCRF	Electronic case report form
DOC	Date of conception
EDC	Electronic data capture
EDD	Estimated date of delivery
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ERB	Ethical review board
EU	European Union
EU PAS	European Union post-authorization study
FDA	Food and Drug Administration
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide-1
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practices
HCP	Healthcare provider
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard ratio
IEC	Independent ethics committee

IPTW	Inverse probability of treatment weighting
IPW	Inverse probability weighting
IRB	Institutional review board
LGA	Large for gestational age
LMP	Last menstrual period
MCM	Major congenital malformations
MRHD	Maximum recommended human dose
NIS	Non-interventional study
PASS	Post-authorization safety study
PS	Propensity score
RA	Receptor agonist
SAB	Spontaneous abortion
SAC	Scientific Advisory Committee
SAE	Serious adverse event
SAP	Statistical analysis plan
SGA	Small for gestational age
SOP	Standard operating procedure
UK	United Kingdom
US	United States
VRCC	Virtual registry coordination center
WHO	World Health Organization

3. Responsible Parties

Sponsor

Eli Lilly and Company

Lilly Corporate Center

Indianapolis, IN 46285, USA

Third Party Vendor

PPD, Part of Thermo Fisher Scientific

929 N Front Street

Wilmington, NC 28401, USA

Contact details and list of investigators are in a standalone document, available upon request.

4. Abstract

Title: Tirzepatide Pregnancy Registry: A Multi-Country Registry-Based Observational Study to Assess Maternal, Fetal, and Infant Outcomes Following Treatment with Tirzepatide for Weight Management During Pregnancy

Version and Date of Protocol: 5.0, see Page 1 for date

Main authors: PPD, part of Thermo Fisher Scientific; Eli Lilly and Company

Rationale and background

Tirzepatide is a glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist. Tirzepatide (Zepbound®, and Mounjaro® in some countries outside of the US) is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with a body mass index (BMI) of 30 kg/m^2 or greater (obesity), or 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition.

There are limited data on the safety of tirzepatide use during pregnancy. Available data are insufficient to identify a potential drug-associated risk of major birth defects, spontaneous abortion, or other adverse maternal or fetal outcomes.

This study is an observational post-authorization safety study (PASS) and is a post-marketing requirement for regulatory authorities.

Research question and objectives

The aim of the Tirzepatide Pregnancy Registry study is to compare the maternal, fetal, and infant outcomes of individuals treated with tirzepatide for weight management during pregnancy (tirzepatide exposed cohort) with outcomes in two comparator cohorts:

- Anti-obesity medication [AOM] active comparator cohort: Individuals who are treated with pharmacotherapy other than tirzepatide or other therapies with GLP-1 receptor agonist (GLP-1 RA) activity for weight management during pregnancy.
- AOM unexposed comparator cohort: Individuals who have obesity or are overweight with at least one weight-related comorbid condition at the time of conception; and who are not treated with tirzepatide, GLP-1 RA therapies, or any other approved products for weight management during pregnancy.

The primary objective is to describe and compare the overall prevalence of major congenital malformations (MCM) among individuals treated with tirzepatide during pregnancy for weight management relative to each of the two comparator cohorts of pregnant individuals (AOM active comparator cohort and AOM unexposed comparator cohort).

The secondary objective is to describe and compare the prevalence of maternal pregnancy complications, fetal and infant outcomes other than MCM, and postnatal growth and development outcomes between pregnant individuals treated with tirzepatide during pregnancy

for weight management and the two comparator cohorts of pregnant individuals (AOM active comparator cohort and AOM unexposed comparator cohort). The secondary outcomes of interest are as follows:

- Maternal pregnancy complications (gestational diabetes, pregnancy-induced hypertension, pre-eclampsia, eclampsia)
- Fetal outcomes (spontaneous abortion, induced abortion, stillbirths)
- Infant outcomes (minor congenital malformation, preterm birth, small-for-gestational age)
- Postnatal growth and development outcomes (postnatal growth deficiency up to one year of age, infant developmental delay up to one year of age)

The exploratory objective is to describe and compare the prevalence of additional maternal, fetal and infant outcomes of interest between pregnant individuals treated with tirzepatide for weight management during pregnancy and the two comparator cohorts of pregnant individuals (AOM active comparator cohort and AOM unexposed comparator cohort). The exploratory outcomes of interest are as follows:

- Hyperemesis gravidarum
- Inadequate gestational weight gain
- Maternal cardiac disease (e.g., heart failure, cardiomyopathies)
- Large-for-gestational age; and
- Infant rapid weight gain

Study design

This is a prospective, observational cohort study designed to evaluate the association between tirzepatide treatment for weight management during pregnancy and subsequent maternal, fetal, and infant outcomes.

Population

The study population will include three cohorts of pregnant individuals:

- Tirzepatide exposed cohort: A cohort of individuals who are treated with tirzepatide for weight management during pregnancy
- Anti-obesity medication (AOM) active comparator cohort: A cohort of individuals who are treated with pharmacotherapy other than tirzepatide or other therapies with GLP-1 RA activity for weight management during pregnancy. The comparator AOMs may include, but not limited to, orlistat, setmelanotide, and naltrexone-bupropion.
- AOM unexposed comparator cohort: A cohort of individuals who have obesity or are overweight with at least one weight-related comorbid condition at the time of conception; and who are not treated with tirzepatide, GLP-1 RA therapies, or any products for weight management during pregnancy.

Variables

Individuals will be considered treated during pregnancy if at least one dose of a product is taken during pregnancy or during the period equal to up to 5 times the product's half-life prior to conception. Based on the half-life of tirzepatide (5 days), individuals will be considered as treated with tirzepatide during pregnancy if a dose is taken within 25 days prior to conception. The primary outcome of MCMs will be adjudicated by independent experts, blinded to exposure, using the CDC's MACDP system or EUROCAT. Secondary and exploratory outcomes will be ascertained by assessment of HCPs who provide care during pregnancy and/or pediatric care.

Covariates of interest will include demographics, risk factors for the study outcomes, comorbidities, concomitant medications, and predictors of treatment with tirzepatide.

Data sources

This study will collect data from participants and HCPs involved in their care or the care of their infants via concise data collection forms at pre-defined timepoints during pregnancy, at pregnancy outcome, and up to 1 year of infant age.

Study size

The study aims to include a minimum of 364 pregnant individuals in each cohort to estimate the prevalence of the primary outcome, MCM, with meaningful confidence and precision and detect a 3-fold increase in the tirzepatide-exposed cohort compared to the AOM active comparator and AOM unexposed comparator cohorts.

Data analysis

Pair-wise comparisons of demographic and baseline characteristics and event rates of the outcomes will be conducted between the study cohorts, as follows:

- Comparison #1: Tirzepatide exposed cohort vs. AOM active comparator cohort
- Comparison #2: Tirzepatide exposed cohort* vs. AOM unexposed comparator cohort
  *Comparison #2 will include a subset of the tirzepatide exposed cohort who have obesity or are overweight with at least one weight-related comorbid condition at the time of conception so as to improve comparability to AOM unexposed comparator cohort with the same obesity-related eligibility criteria.

The prevalence of each outcome will be calculated by dividing the number of cases of the outcome by the appropriate denominator for that particular outcome, along with 95% confidence interval (CI). For most outcomes, the analysis population (denominator) will be the number of pregnant individuals, number of pregnant individuals with pregnancy outcome data, the number of live births, or the number of infants with follow-up data at the time point of interest, as appropriate; however, for some outcomes, the analysis population (denominator) will be restricted based on certain relevant factors.

Formal quantitative comparisons of the event rates of the outcomes of interest will be conducted between the tirzepatide exposed and each of the two comparator cohorts. For each outcome, if

the number of events permits, results will be presented for both unadjusted and adjusted models. Summary statistics (relative risk) will be reported along with their 95% CIs and p-values. Adjusted methods will incorporate weights estimated using the stabilized inverse probability of treatment weighting (IPTW) method to balance the cohorts regarding observable covariates. Where sample size permits, subgroup analyses will be conducted considering the timing and extent of exposure.

Milestones

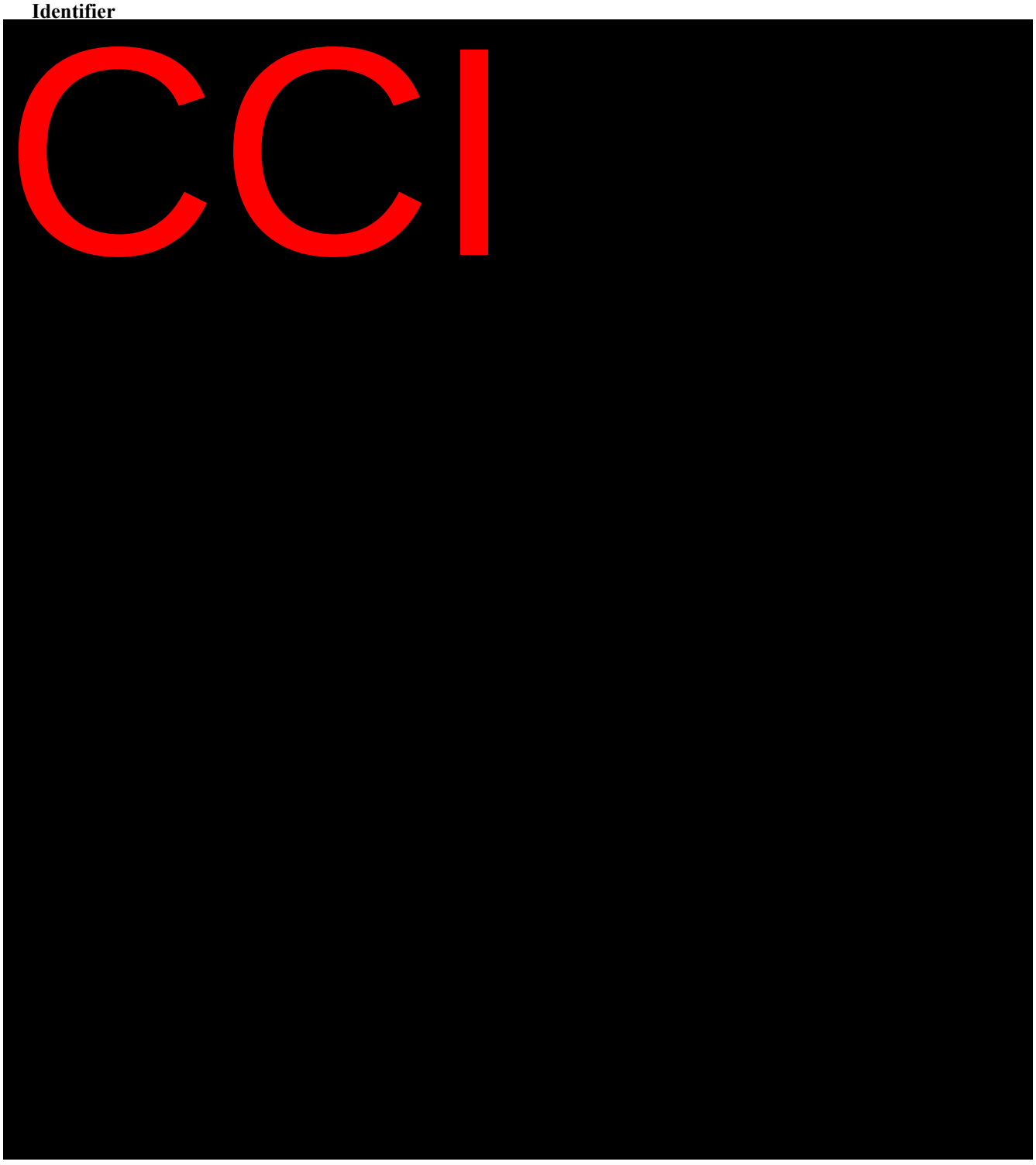
Start of data collection is planned for 28 Sep 2025. The final study report is planned for submission to appropriate regulatory authorities by 30 June 2036.

5. Amendments and Updates

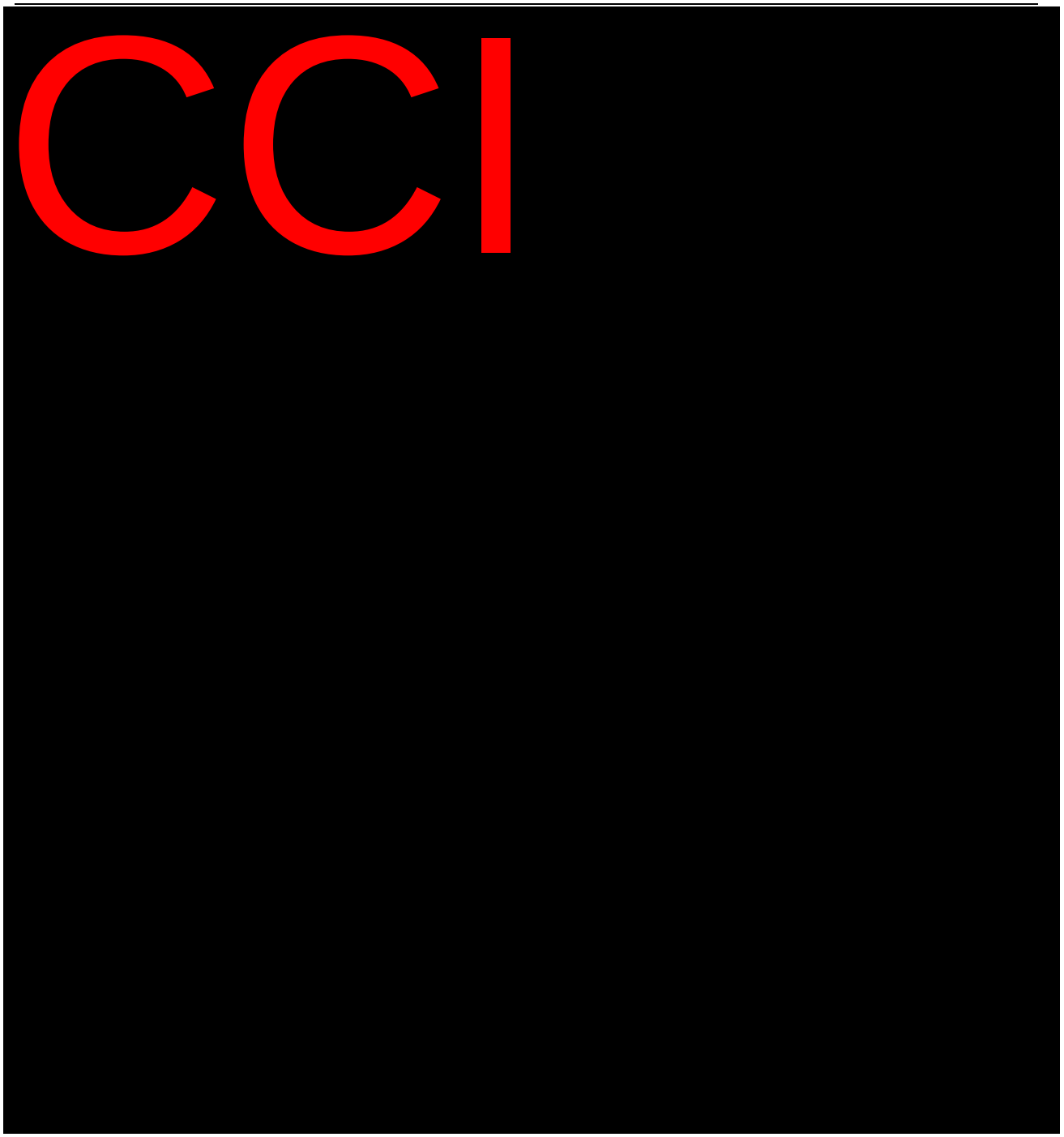
The table below summarizes the list of updates made to the protocol incorporating the feedback received from the FDA.

Amendment or Update Identifier	Date	Section of Study Protocol	Amendment or Update	Reason
CCI				

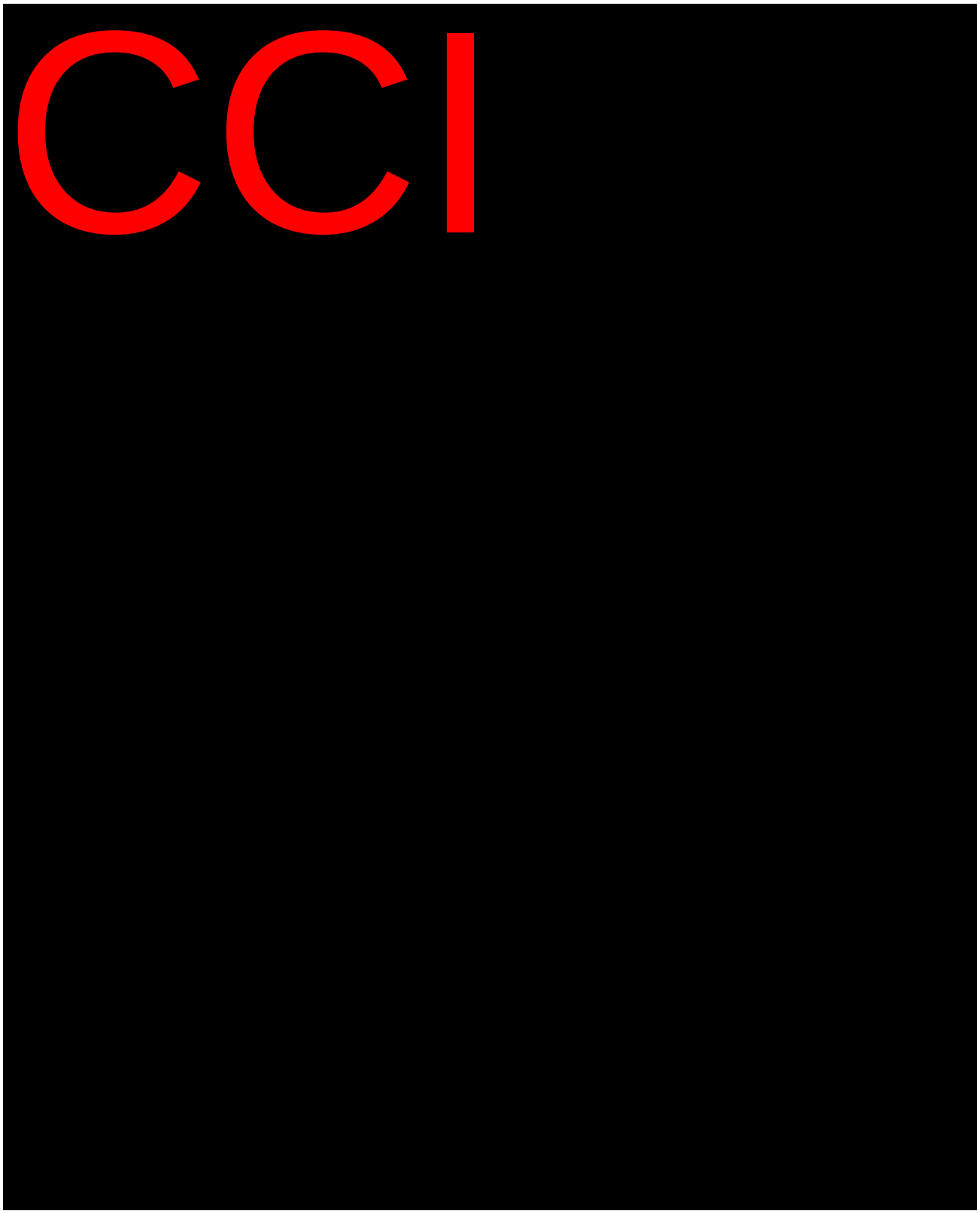
Amendment or Update Identifier	Date	Section of Study Protocol	Amendment or Update	Reason



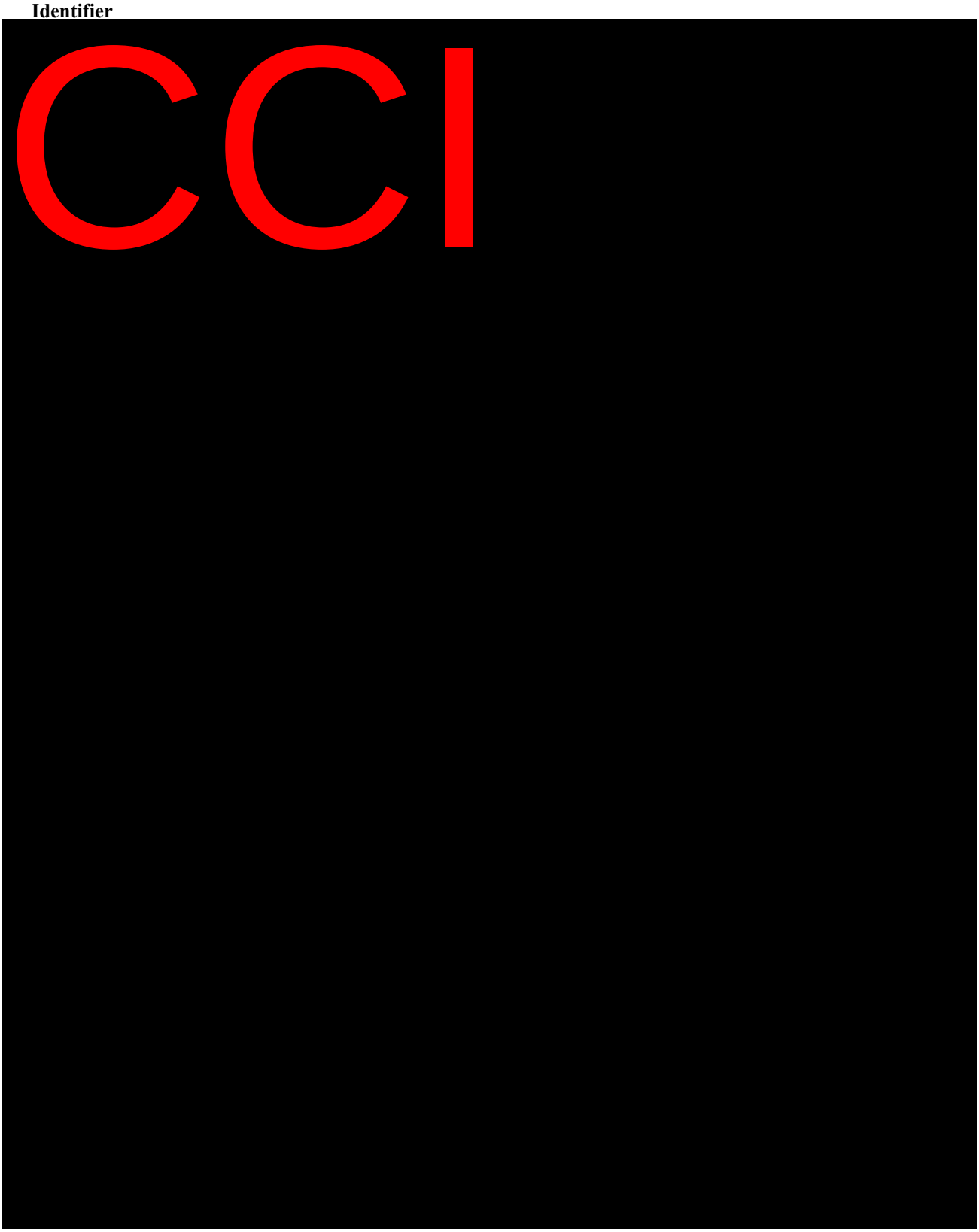
Amendment or Update Identifier	Date	Section of Study Protocol	Amendment or Update	Reason



Amendment or Update Identifier	Date	Section of Study Protocol	Amendment or Update	Reason



Amendment or Update Identifier	Date	Section of Study Protocol	Amendment or Update	Reason



Amendment or Update Identifier	Date	Section of Study Protocol	Amendment or Update	Reason

6. Milestones

Milestone	Planned date
Draft protocol	30 June 2024
Final protocol	30 June 2025
Start of data collection/Study launch	28 September 2025
End of data collection	30 June 2035
Interim report 1 submission [a]	30 June 2026
Interim report 2 submission	30 June 2028
Interim report 3 submission	30 June 2030
Interim report 4 submission	30 June 2032
Interim report 5 submission	30 June 2034
HMA-EMA Catalogues of real-world data sources and studies register	Prior to start of data collection
Study completion	30 June 2035
Final report of study results submission	30 June 2036

Abbreviation: HMA-EMA = Heads of Medicines Agencies European Medicines Agency.

[a] Interim reports may include the number of patients who have entered the study, descriptive patient information, the number of patients with outcomes, and recruitment efforts.

7. Rationale and Background

7.1. Study Rationale

The aim of this study is to compare maternal, fetal, and infant outcomes among patients treated with tirzepatide (Zepbound® or Mounjaro® in some countries outside of the United States [US]) for chronic weight management during pregnancy relative to an untreated reference population. The study is an observational post-authorization safety study (PASS) and is a post-marketing requirement for regulatory authorities.

The Tirzepatide Pregnancy Registry study will add to the current body of knowledge regarding the safety of tirzepatide exposure during pregnancy. Available human data on tirzepatide exposure during pregnancy are insufficient to inform benefit/risk assessment. The registry will provide information on maternal, fetal, and infant outcomes following treatment with tirzepatide during pregnancy so that patients and healthcare providers (HCPs) can make informed treatment decisions.

7.2. Tirzepatide for Chronic Weight Management

Tirzepatide is a glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist (GLP-1 RA).[1] Tirzepatide lowers body weight with greater fat mass loss than lean mass loss. Tirzepatide decreases calorie intake, and the effects are likely mediated by affecting appetite. Tirzepatide is a once-weekly subcutaneous injection. Tirzepatide is based on the GIP sequence and contains aminoisobutyric acid (AiB) in positions 2 and 13, a C-terminal amide, and Lys residue at position 20 that is attached to 1,20-eicosanedoic acid via a linker. The empirical formula is $C_{225}H_{348}N_{48}O_{68}$.[1]

Tirzepatide is approved as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of 30 kg/m^2 or greater (obesity), or 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes mellitus, obstructive sleep apnea, or cardiovascular disease).

7.3. Evidence to Date Concerning Pregnancy Exposure to Tirzepatide

7.3.1. Animal Studies

In pregnant rats given twice-weekly subcutaneous doses of 0.02, 0.1, and 0.5 mg/kg tirzepatide [0.03-, 0.07-, and 0.5-fold the maximum recommended human dose (MRHD) of 15 mg once weekly based on area under the curve (AUC)] during organogenesis, increased incidences of external, visceral, and skeletal malformations, increased incidences of visceral and skeletal developmental variations, and decreased fetal weights were observed coincided with pharmacologically-mediated reductions in maternal body weights and food consumption.

In pregnant rabbits given once-weekly subcutaneous doses of 0.01, 0.03, or 0.1 mg/kg tirzepatide (0.1-, 0.06-, and 0.2-fold the MRHD) during organogenesis, pharmacologically mediated effects

on the gastrointestinal system resulting in maternal mortality or abortion in a few rabbits occurred at all dose levels. Reduced fetal weights associated with decreased maternal food consumption and body weights were observed at 0.1 mg/kg.

In a pre- and post-natal study in rats administered subcutaneous doses of 0.02, 0.10, or 0.25 mg/kg tirzepatide twice weekly from implantation through lactation, F1 pups from F0 maternal rats given 0.25 mg/kg tirzepatide had statistically significant lower mean body weight when compared to controls from post-natal day 7 through post-natal day 126 for males and post-natal day 56 for females.[1]

7.3.2. Clinical Trial Data

A Phase 1 study of tirzepatide in healthy lactating females (NCT05978713) has shown that following a single 5-mg dose, the concentration of tirzepatide in breastmilk was found to be undetectable to very low compared to plasma concentrations. Because tirzepatide is an amino acid sequence, any low amount present in breastmilk is expected to be degraded and not orally absorbed as intact drug by the breastfed infant.[2] On the other hand, there are currently no clinical data available for exposure to tirzepatide given subcutaneously during pregnancy. Clinical trials that assessed the efficacy of tirzepatide for the treatment of obesity among adults excluded pregnant individuals, and use of contraception was required for individuals of child-bearing potential during the study.[3-6] Therefore, the potential risk of tirzepatide treatment during pregnancy remains unknown.

7.3.3. Epidemiological Data

The effects of tirzepatide use during pregnancy on maternal, fetal, and infant outcomes are not well characterized. A recent multi-national observational study including more than 50,000 pregnant women exposed to GLP-1 RAs early during pregnancy for the treatment of diabetes did not report an increased risk for MCMs (cleft palate and hydrocephalus); however, the study did not include women exposed to tirzepatide.[7] Another multicenter study of 168 pregnant women exposed to GLP-1 RAs (liraglutide, semaglutide, dulaglutide, and exenatide) and two reference groups (156 pregnant women with diabetes and 163 pregnant women with obesity or overweight) also found no increased risk of major birth defects or pregnancy losses associated with exposure.[8]

7.4. Overweight and Obesity

7.4.1. Description and Epidemiology

Obesity is defined as abnormal or excessive fat accumulation that may impair health. According to the World Health Organization (WHO) classification system, overweight in adults is defined as a BMI of ≥25 kg/m^2, and obesity is classified as a BMI of ≥30 kg/m^2.[9]

Worldwide, obesity has tripled over the last 50 years, and in 2022, 2.5 billion adults (aged >18 years) were overweight; of these, over 890 million were living with obesity, representing one in eight people in the world.[9] Globally, obesity is now considered one of the most significant public health challenges.[10,11]

Individuals of childbearing age (15 to 44 years) are particularly vulnerable to weight gain, and weight gain during this time is strongly associated with adverse health outcomes later in life.[12-15] Pre-pregnancy obesity rates among females aged 15 to 44 years are reported to be around 25% in the US. However, there is significant variation by race/ethnicity. Pre-pregnancy obesity rates are higher for non-Hispanic black (36.2%) and Hispanic individuals (30.5%) compared to non-Hispanic white (24.8%) and Asian (18.6%) individuals.[16] Obesity during the childbearing years has been associated with adverse pregnancy outcomes for the mother (e.g., gestational diabetes, pregnancy-induced hypertension, pre-eclampsia, stillbirth, emergency cesarean delivery, and postpartum depression), as well as for the babies (e.g., pre-term birth, and babies who are large for gestational age).[17-19]

7.4.2. Implications of Overweight or Obesity for Pregnancy Complication and Fetal and Infant Outcomes

Maternal obesity is associated with an increased risk of adverse pregnancy outcomes, including spontaneous abortion (SAB) and stillbirth.[20,21] For stillbirth, the risk appears to increase in a stepwise fashion with each increase in BMI category (30.0–34.9, 35.0–39.9, 40+, 50+) and the relative risk is higher in black women as compared to white women (hazard ratio [HR] for black women with obesity vs. black women without obesity: 1.9; HR for white women with obesity vs. white women without obesity: 1.4).[21] Maternal obesity is also associated with increased risk of adverse neonatal outcomes, including preterm birth, macrosomia, and a variety of birth defects. Studies have observed associations between maternal obesity and cardiovascular anomalies, limb reduction anomalies, orofacial anomalies, neural tube defects, and hydrocephaly.[22-25] In a recent population-based cohort study using Swedish national registries, compared with offspring of mothers with a weight in the normal range, the risk ratio of major congenital malformations (MCM) increased with maternal BMI: 1.05 in mothers with overweight (BMI, 25 to <30 kg/m^2), 1.12 in mothers in obesity class I (BMI, 30 to <35 kg/m^2), 1.23 in mothers in obesity class II (BMI, 35 to <40 kg/m^2), and 1.37 in mothers in obesity class III (BMI ≥40 kg/m^2).[26]

Maternal obesity is further associated with an increased risk for pregnancy complications including pregnancy induced hypertension, gestational diabetes, and pre-eclampsia.[27-29] In a prospective cohort study using data from the Prenatal Exposures and Preeclampsia Prevention, the risk for pre-eclampsia doubled at a BMI of 26 kg/m^2 (OR 2.1) and nearly tripled at a BMI of 30 kg/m^2 (OR 2.9) compared with women with a BMI of 21 kg/m^2.[27] Reports also indicate an association between maternal obesity and hyperemesis gravidarum (HG). Data from the Norwegian Mother and Child, Cohort Study of 71,468 women indicated that women with obesity or overweight had slightly increased risk (prevalence of 1.5% vs. 1.0%) to develop HG during pregnancy compared to women with normal weight.[30]

Maternal obesity has also been associated with longer-term infant adverse effects including rapid infant weight gain and developmental adverse effects. Data from the Healthy Start Study in 414 mother-infants pairs indicated that maternal pre-pregnancy BMI had a positive association with rapid infant weight gain,[31] which has been considered a predisposing factor for childhood obesity and subsequent cardiometabolic risk.[32] Analysis of two prospective cohorts (the British

Avon Longitudinal Study of Parents and Children; and the Dutch Generation R) that included more than 7,000 parents and their offspring reported an association between pre-pregnancy maternal overweight and reduced child verbal skills. Pre-pregnancy maternal overweight was associated with an 8% increased risk for reduced non-verbal skills; however, this association was not significant after statistical adjustment.[33]

7.4.3. Current Standard of Care

Although lifestyle modifications continue to be the first-line treatment for obesity, most people with obesity struggle to achieve and maintain weight loss with diet and exercise alone.[34-39]

Surgical treatments offer an effective alternative for some people with severe obesity, but bariatric surgery carries a risk in connection with the procedure and is not without post-surgical complications. Pharmacotherapy may therefore serve as a valuable adjunct to lifestyle intervention for individuals with obesity to achieve and sustain clinically relevant weight loss, improve comorbid conditions, and facilitate a healthier lifestyle.[34,36,39]

As of 25 January 2025, a limited number of pharmacological options, including therapies with GLP-1 RA activity: semaglutide, tirzepatide, liraglutide; and non-GLP-1 RAs: orlistat, naltrexone-bupropion, setmelanotide, phentermine, phentermine-topiramate are approved for weight management in the US and the European Union (EU). All of these have shown effective weight loss, but generally only in the range of around 5% to 10% except for semaglutide and tirzepatide. The STEP 1 (NN9536-4373) trial data showed that treatment with semaglutide 2.4 mg resulted in a weight loss of up to 14.9% compared with 2.4% in the placebo group (treatment policy estimand).[40] SURMOUNT-1 (NCT04184622) data demonstrated that treatment with tirzepatide resulted in a higher weight loss of 20.9% at week 72 with 15 mg weekly doses compared with 3.1% in the placebo group (treatment regimen estimand).[5]

Additionally, since semaglutide and tirzepatide are administered once weekly, they offer a more convenient treatment option than existing weight management drugs and may improve treatment adherence.[5,6] During pregnancy, lifestyle modifications are the primary tool for weight management.[41-43] Weight loss during pregnancy is generally discouraged and use of surgical and pharmacologic interventions are not recommended during, or immediately preceding, pregnancy due to known or suspected safety concerns as well as lack of data on safety of use during pregnancy.[44]

Currently patients are advised to discontinue tirzepatide when pregnancy is recognized. However, it is expected that exposure during pregnancy may occur among real-world patients being treated for chronic weight management.

8. Research Question and Objectives

The aim of the Tirzepatide Pregnancy Registry study is to compare the maternal, fetal, and infant outcomes of individuals treated with tirzepatide for weight management during pregnancy (tirzepatide exposed cohort) with outcomes in two comparator cohorts:

- Anti-obesity medication [AOM] active comparator cohort: Individuals who are treated with pharmacotherapy other than tirzepatide or other therapies with GLP-1 receptor agonist (GLP-1 RA) activity for weight management during pregnancy. The comparator AOMs may include, but not limited to, orlistat, setmelanotide, and naltrexone-bupropion.
- AOM unexposed comparator cohort: Individuals who have obesity or are overweight with at least one weight-related comorbid condition at the time of conception; and who are not treated with tirzepatide, GLP-1 RA therapies, or any products for weight management during pregnancy.

8.1. Primary Objective

The primary objective is to describe and compare the overall prevalence of MCM among individuals treated with tirzepatide for weight management during pregnancy relative to each of the two comparator cohorts of pregnant individuals (AOM active comparator cohort and AOM unexposed comparator cohort).

8.2. Secondary Objective

The secondary objective is to describe and compare the prevalence of maternal pregnancy complications, fetal and infant outcomes other than MCM, and postnatal growth and development outcomes between pregnant individuals treated with tirzepatide for weight management during pregnancy and the two comparator cohorts of pregnant individuals (AOM active comparator cohort and AOM unexposed comparator cohort). The secondary outcomes of interest are as follows:

Maternal pregnancy complications

- Gestational diabetes
- Pregnancy-induced hypertension
- Pre-eclampsia
- Eclampsia

Fetal outcomes

- Spontaneous abortion (SAB)
- Induced abortion
- Stillbirth

Infant outcomes

- Overall minor congenital malformations
- Preterm birth
- Small for gestational age (SGA)

Postnatal growth and development outcomes

- Postnatal growth deficiency (up to one year of age)
- Infant developmental delay (up to one year of age)

8.3. Exploratory Objective

The exploratory objective is to describe and compare the prevalence of additional maternal, fetal, and infant outcomes of interest between pregnant individuals treated with tirzepatide for weight management during pregnancy and the two comparator cohorts of pregnant individuals (AOM active comparator cohort and AOM unexposed comparator cohort). The exploratory outcomes of interest are as follows:

Maternal pregnancy complications

- Hyperemesis gravidarum (HG)
- Inadequate gestational weight gain (GWG)
- Maternal cardiac disease (e.g., heart failure, cardiomyopathies)

Infant outcome

- Large for gestational age (LGA)
- Rapid infant weight gain (up to one year of age)

9. Research Methods

9.1. Study Design

The Tirzepatide Pregnancy Registry study is a multi-country, prospective, observational cohort study designed to evaluate the association between tirzepatide exposure during pregnancy and subsequent maternal, fetal, and infant outcomes. The registry will enroll participants in the US, the United Kingdom (UK), and Germany. Registry enrollment will be monitored and further expansion to include additional countries will be considered as needed. Participation in the registry is voluntary, and participants can withdraw their consent to participate at any time. Data will be collected from enrolled pregnant individuals and the HCPs involved in their care or the care of their infants, if applicable. The registry is strictly observational; the schedule of office visits and all treatment regimens will be determined by HCPs. No additional laboratory tests or HCP assessments will be required as part of this registry. The design of this pregnancy registry follows current FDA guidance for designing and implementing pregnancy exposure registries.[45]

9.2. Primary Outcome

The primary outcome for the study is MCMs.

9.3. Secondary Outcomes

The secondary outcomes for the study include the following:

- Gestational diabetes
- Pregnancy-induced hypertension
- Pre-eclampsia
- Eclampsia
- SAB
- Induced abortion
- Stillbirth
- Preterm birth
- SGA
- Minor congenital malformations
- Postnatal growth deficiency
- Infant developmental delay

9.4. Exploratory Outcomes

The exploratory outcomes for the study include the following:

- HG
- Inadequate GWG
- Maternal cardiac disease (e.g., heart failure, cardiomyopathies)
- Large for gestational age (LGA)
- Rapid infant weight gain (up to 1 year of age)

The definitions and ascertainment of these outcomes are provided in Section 9.7.3.

9.5. Setting

9.5.1. Study Population

After appropriate alignment with a regulatory authority (e.g., FDA) and institutional review board (IRB)/independent ethics committee (IEC) approval of the protocol, enrollment of individuals in the registry will begin. The registry will enroll patients for up to 10 years, and the enrollment period may be extended if the target sample size is not met, and shortened if the target is met ahead of schedule.

For each enrolled pregnant individual, participation will begin at the time of providing informed consent and end either at pregnancy outcome (if fetal loss – SAB, stillbirth, or induced abortion) or 12 months after pregnancy outcome (if live birth). For each live born infant of prospectively enrolled participants, infant follow-up will begin at birth and end at 12 months of age. For each live born infant of retrospectively enrolled participants, infant follow-up will begin at the time of enrollment and end at 12 months of age; data will be collected retrospectively from time of enrollment to birth outcome. Maternal and fetal outcomes will be assessed through the end of pregnancy, and infant outcomes will be assessed through 12 months of infant age. However, pregnancy outcomes prior to first contact with the Virtual Registry Coordination Center (VRCC) (i.e., retrospectively enrolled participants) will be excluded in the main analysis (Section 9.5.2).

The study population will include three cohorts of pregnant individuals:

- Tirzepatide exposed cohort: A cohort of individuals who are treated with tirzepatide for weight management during pregnancy.
- Anti-obesity medication (AOM) active comparator cohort: A cohort of individuals who are treated with pharmacotherapy other than tirzepatide or other therapies with GLP-1 RA activity for weight management during pregnancy. The comparator AOMs may include, but not limited to, orlistat, setmelanotide, and naltrexone-bupropion.
- AOM unexposed comparator cohort: A cohort of individuals who have obesity or are overweight in the presence of at least one weight-related comorbid condition at the time of conception; and who are not treated with tirzepatide, GLP-1 RA therapies, or any products for weight management during pregnancy.

9.5.2. Inclusion and Exclusion Criteria

For an eligible participant, all inclusion criteria must be answered ‘yes’, and all exclusion criteria must be answered ‘no’. Table 9.1 summarizes the inclusion and exclusion criteria for the cohorts.

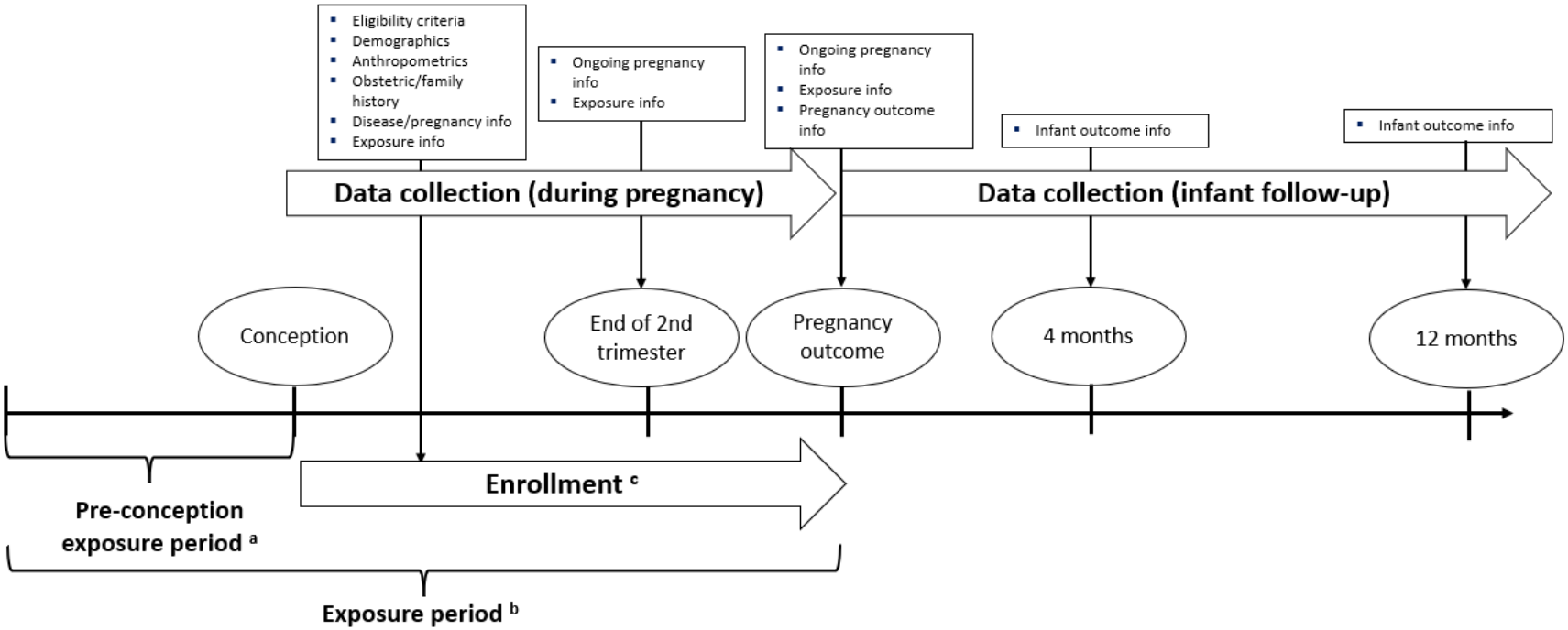
Table 9.1. Study Population

Cohort	Inclusion Criteria[a]	Exclusion Criteria[a]
Tirzepatide exposed cohort: A cohort of individuals who are treated with tirzepatide for weight management during pregnancy[b,c,d]	• Signed consent obtained before any study-related activities • AFAB 15-≤50 years of age at the time of signing consent • Currently or recently (within 12 months) pregnant • Resident of country included in the study • Authorization for their HCP(s) to provide data to the registry • *Exposure to at least one dose of tirzepatide for weight management at any time during pregnancy[b,c]* • *Prescribed the qualifying AOM for treatment of obesity[e] or overweight with at least one weight-related comorbid condition[f]*	• None[c,d]
AOM active comparator cohort: A cohort of individuals who are treated with pharmacotherapy other than tirzepatide or other therapies with GLP-1 RA activity for weight management during pregnancy.[b] The comparator AOMs may include, but are not limited to, orlistat, setmelanotide, and naltrexone-bupropion	• Signed consent obtained before any study-related activities • AFAB 15-≤50 years of age at the time of signing consent • Currently or recently (within 12 months) pregnant • Resident of country included in the study • Authorization for their HCP(s) to provide data to the registry • *Exposure to at least one dose of AOM other than tirzepatide or other therapies with GLP-1 RA activity at any time during pregnancy[d]* • *Prescribed the qualifying AOM for treatment of obesity[e] or overweight with at least one weight-related comorbid condition[f]*	• *Exposure to tirzepatide or other therapies with GLP-1 RA activity at any time during pregnancy[b]*
AOM unexposed comparator cohort: A cohort of individuals who have obesity or are overweight with at least one weight-related comorbid condition at the time of conception and who are not treated with tirzepatide, GLP-1 RA therapies, or any other approved products for weight management, during pregnancy[b]	• Signed consent obtained before any study-related activities • AFAB 15-≤50 years of age at the time of signing consent • Currently or recently (within 12 months) pregnant • Resident of country included in the study • Authorization for their HCP(s) to provide data to the registry • *Have obesity[f] or overweight with at least one weight-related comorbid condition[g] at time of conception*	• *Exposure to tirzepatide or other therapies with GLP-1 RA activity at any time during pregnancy[b]* • *Exposure to any other pharmacotherapies for weight management[e] at any time during pregnancy[b]*

Abbreviations: AFAB = assigned female at birth; AOM = anti-obesity medication; BMI = body mass index; DOC = date of conception; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HCP = healthcare provider; LMP = last menstrual period; VRCC = virtual registry coordination center

[a] Text italicized to highlight differences between cohorts.
[b] Participants will be considered exposed to tirzepatide or other therapies with GLP-1 RA activity or other products during pregnancy if a dose is taken up to 5 half-lives prior to the DOC (LMP + 14 days). Participants who are exposed to tirzepatide or other therapies with GLP-1 RA activity before pregnancy, but more than the 5 half-lives prior to DOC may be eligible for enrollment into the comparator cohort, if they fulfil certain eligibility criteria.
[c] Individuals prescribed tirzepatide for reasons other than weight management can be enrolled into the current study, but they are not the focus of the current protocol and will be excluded from the main analysis population (see Section 9.11.1.1.2).
[d] In some countries, only patients prescribed tirzepatide according to the approved indications may be included, in accordance with local regulations.
[e] Eligible comparator medications at this time include orlistat, setmelanotide, and naltrexone-bupropion. Newly approved medications will be reviewed regularly and added if applicable.
[f] Obesity defined as: BMI ≥30 kg/m^2
[g] Overweight defined as BMI ≥27 kg/m^2 and at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes mellitus, obstructive sleep apnea, or cardiovascular disease).

The study aims for inclusive enrollment by incorporating only inclusion criteria common for observational studies, with minimal exclusion criteria. To address potential biases and confounding, the main analysis population for the study will be further limited to individuals who are prospectively enrolled (prior to pregnancy outcome), not exposed to known teratogens and/or investigational medications during pregnancy, not exposed to other GLP-1 RA therapies during pregnancy or within 5-times the half-life of the drug prior to conception, not lost to follow-up, and not already included in the analysis population for a prior pregnancy. The definitions of the main analysis population and the rationale are provided in Section 9.11.1.1.



[a] Time to product elimination (5 times terminal half-life); tirzepatide half-life = 5 days; therefore, time to elimination = 25 days
[b] If a participant is exposed to the product during this period, they will be considered exposed during pregnancy
[c] Participants may be retrospectively enrolled into the registry up to one year after pregnancy outcome but will not be included in main analysis

Figure 9.1. Study flow chart.

9.6. Data Collection

Enrolled pregnant individuals and the HCPs involved in their care or the care of their infants, if applicable, will serve as data reporters to the registry. It is anticipated that most obstetric data will be provided by the individual's obstetric HCP, defined as any HCP who provides care during pregnancy (e.g., obstetrician, family practitioner, general practitioner, midwife), and that the majority of pediatric data will be provided by the infant's pediatric HCP, defined as any HCP who provides pediatric care (e.g., pediatrician, family practitioner, general practitioner). PPD may also request data from other HCPs involved in the individual's or infant's care (e.g., prescriber, specialist, midwife) after appropriate medical release is obtained from the individual.

The data collection process for each participant will begin at enrollment, and cumulative data throughout the pregnancy will be collected at three time points: enrollment, end of the second trimester (approximately 26 gestational weeks), and pregnancy outcome (live birth or fetal loss). For live-born infants, data from pediatric visits will be collected at two time points: 4 months and 12 months after delivery (Figure 9.1). Data collection efforts will be identical for all enrolled pregnant individuals and their infants regardless of their exposures and study cohort assignment.

At enrollment, once consent, registration information (including eligibility criteria), reporter contact information, and medical releases have been provided by the pregnant individual, maternal demographic characteristics, pre-pregnancy anthropometrics, maternal obstetrical history, and family history of congenital malformations will be collected. These data will be collected on the ***Registration Form for Participants***. Registration information, including eligibility criteria, will be confirmed by HCP(s), as appropriate. The HCP(s) will additionally provide maternal pre-pregnancy anthropometrics, maternal obstetrical history, family history of congenital malformations, disease information, pregnancy information, and maternal exposures during pregnancy. All of these data will be collected on the ***Registration Form for Healthcare Providers*** and ***Pregnancy Information Form***. At approximately the end of the second trimester, the HCP(s) will be asked to complete another ***Pregnancy Information Form***, which will collect any updates to pregnancy information and maternal exposures during pregnancy. Around or after the estimated date of delivery (EDD) or after a known pregnancy outcome, the HCP(s) will be asked to complete another ***Pregnancy Information Form as*** well as the ***Pregnancy Outcome Form***, which will collect pregnancy outcome information. For each live-born infant, the pediatric HCP will be asked to complete an ***Infant Outcomes Form***, which will collect infant information, including infant growth and development data, at two time points: at approximately 4 and 12 months after delivery. These visits align with the recommended infant well-child visit (health visitor check) schedules in the study countries.[45,46]

If a congenital malformation (major or minor) or other event of interest is reported, additional information may be requested from the reporting HCP on the ***Targeted Follow-up Form*** to properly characterize the event. The date each data collection form is completed will also be collected.

Table 9.2 provides a summary of the data collection process, including the forms that will be used to collect the data, the timing for completion of each form, the potential reporters or sources

of the data, and the types of data that will be collected. Section 9.6 provides additional details regarding the data collected. Various approaches may be considered to reduce both healthcare practitioner and participant burden around data collection, and may include use of smart phone applications or other technologies, as appropriate.

Table 9.2. Summary of Data Collection Process

Data Collection Form	Data Sources/Reporters[a]	Timing of Completion	Data Collected[b]
Registration Form for Participants	Participant	Enrollment	Registration information, including eligibility criteria Maternal demographic characteristics Maternal pre-pregnancy anthropometrics Maternal obstetrical history Family history of congenital malformations
Registration Form for HCPs	Obstetric HCP and prescribing HCP, if needed	Enrollment	Registration information, including eligibility criteria Maternal pre-pregnancy anthropometrics Maternal obstetrical history Family history of congenital malformations Disease information Baseline pregnancy information
Pregnancy Information Form	Obstetric HCP and prescribing HCP, if needed	Enrollment, end of second trimester[c], and EDD/pregnancy outcome[c]	Ongoing pregnancy information Maternal exposures during pregnancy
Pregnancy Outcome Form	Obstetric HCP and pediatric HCP, if needed	EDD/pregnancy outcome	Pregnancy outcome information
Infant Outcomes Form	Pediatric HCP	4 and 12 months after delivery	Infant outcome information at 4 and 12 months
Targeted Follow-up Form	Obstetric, pediatric, or other HCP	Any time after pregnancy outcome	Targeted follow-up information

Abbreviations: EDD = estimated date of delivery; HCP = healthcare provider

[a] The primary data source is determined by a hierarchy that is variable specific (e.g., prescribing provider would be primary for disease and exposure information and the obstetric HCP would be primary for pregnancy information). Patients may provide information freely at any point and be considered an initial reporter. However, these data would not be used in the analysis unless or until the HCP confirms and provides additional follow-up as needed.

[b] Data collected at each study site will abide by regulatory guidelines, local privacy laws, and national provisions (e.g., date of birth and race/ethnicity will not be collected from participants in Germany). The collection of race and ethnicity data in the US will comply to the FDA guidance for industry, Collection of Race and Ethnicity Data in Clinical Trials and Clinical Studies for FDA-Regulated Medical Products.[47]

[c] Obtain updated information since the previous contact.

9.6.1. Attempts to Obtain Follow-up Information

In the month that the follow-up is due, the HCP will be contacted by PPD and asked to provide follow-up information. If needed, three subsequent attempts will be made approximately every 2 weeks via various modes of communication. If no response is received from the HCP, additional attempts may occur at the next planned data collection time point (e.g., at pregnancy

outcome). When appropriate, the participant will be asked to encourage their HCP to provide the missing data. A final communication to obtain follow-up data will take place indicating that the participant will be considered lost to follow-up if no further data are received. If at any point in the follow-up process the participant withdraws consent or the HCP indicates that the participant is lost to follow-up, no further attempts will be made. The reason the participant was lost to follow-up (e.g., no response from HCP, no response from participant, or participant withdrawal of consent) will be documented.

9.6.2. Follow-up Process for Clarification for Information

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

9.6.3. Awareness and Retention

9.6.3.1. Awareness Strategy

An active, targeted, multi-pronged awareness campaign will be employed to recruit participants for the registry. The campaign will focus on:

- Pregnant individuals
- Individuals who have a diagnosis of obesity or overweight with at least one weight-related comorbid condition
- Individuals using tirzepatide or other products for weight management
- Obstetric HCPs
- HCPs who are likely to treat patients with diagnoses of obesity or overweight with at least one weight-related comorbid condition
- HCPs who are likely to prescribe tirzepatide or other products for weight management (including, but not limited to, other therapies with GLP-1 RA activity).

As described in Section 7.4.1, non-Hispanic black and Hispanic individuals are at an increased risk of pre-pregnancy obesity compared to non-Hispanic white and Asian individuals; therefore, the sponsor will make efforts to improve enrollment of participants from underrepresented racial and ethnic populations in this study.

Obstetric HCPs and HCPs who are likely to treat patients with obesity may be identified via HCP directories and/or professional associations. If appropriate and/or needed, pregnant individuals, patients who have a diagnosis of obesity or overweight with at least one weight-related comorbidity, and patients using tirzepatide may be identified through patient support groups and external data sources, such as pharmacy/medical claims or electronic medical records. If appropriate, the sponsor's existing infrastructure for distributing tirzepatide and supporting stakeholders may be leveraged to identify HCPs who are known to prescribe tirzepatide and pregnant individuals who have been exposed to tirzepatide.

To start, the primary aim of the registry's awareness strategy will be to recruit individuals exposed to tirzepatide during pregnancy. Once the characteristics of a portion of the tirzepatide-exposed participants are understood, the awareness campaign for the comparator cohort will be tailored to increase comparability of the cohorts. In addition, individuals who were exposed to tirzepatide before (>25 days prior to date of conception [DOC]) but not during pregnancy (≤25 days prior to DOC to pregnancy outcome) will be targeted for enrollment into the comparator cohort.

A multi-modal approach will be used to deliver registry education and awareness materials to targeted HCPs and patients. This approach involves direct-to-HCP outreach as well as online and print advertising directed to both HCPs and patients. In addition, stakeholders may be identified and provided with information regarding the registry via telephone through the Medical Information Contact Centre and/or the patient assistance program. Other relevant approaches and/or stakeholders may be implemented, as needed, to deliver registry education and awareness materials.

All strategies around registry awareness campaigns and materials will comply with local laws and regulations.

Direct-to-HCP Outreach

Direct-to-HCP outreach will be achieved by delivering awareness materials to targeted HCPs via email, fax, and/or hardcopy mail. In addition, the sponsor's representatives may provide registry education and recruitment materials to HCPs in person. HCPs will be asked to identify potential registry participants and encourage their participation by speaking to them about the registry and providing them with the patient-directed registry recruitment materials.

Digital Advertising

Information regarding the registry and the registry recruitment materials will also be available online. A registry-specific website will be developed, where all recruitment materials will be available for download. This website will be accessible through the tirzepatide website and discoverable in any internet browser by performing a search related to pregnancy and tirzepatide, tirzepatide, and/or weight management. Information regarding the registry and/or a link to the registry website may also be available on the following websites:

- FDA listing of pregnancy registries on FDA website
- Clinical trials database website
- Society for Maternal-Fetal Medicine listing of registries
- PPD website

A web-based interface compatible with both computers and mobile devices will also be developed to improve information accessibility and enable broader participation. As deemed necessary, online advertisements on social media sites or other relevant websites (e.g., professional association websites or websites commonly visited by pregnant individuals) may be used to direct potential participants to the registry website. Targeted advertisements on web-

based applications frequented by pregnant individuals will be strategically implemented to drive registry awareness.

Print Advertising

Various print materials will also be used to provide information related to the registry and to facilitate recruitment. The tirzepatide prescribing information provides registry information, including contact information (US requirement only). Information related to the registry also may be directed to HCPs via announcements/publications in relevant professional journals/newsletters or presentations/exhibits at relevant professional meetings. As deemed necessary, print advertisements in newspapers or magazines with targeted patients among their readership may be used to direct potential participants to the registry, and recruitment materials may be distributed to locations commonly frequented by targeted patients (e.g., ultrasound clinics, weight-loss centers).

Awareness Materials

In addition to the registry information in the product label, educational materials designed to elicit interest in registry participation will be developed. All messaging will be aligned with the product label and will be balanced to ensure that it does not unintentionally promote the use of tirzepatide for chronic weight management during pregnancy. Materials may include the following:

- An information sheet and/or brochure that will briefly describe the registry purpose and procedures, including the incentives for participation
- Information on how to access the registry web-based/mobile application
- Registration form and sample participant consent form
- Prescribing information
- Participant consent-to-contact card (this card enables the VRCC to contact the potential participant and provide additional information about the registry)

9.6.3.2. Retention Strategy

A retention strategy, facilitated by engaging both the participant and HCP, will seek to minimize the reporting burden on these groups to the extent possible.

The registry staff will serve as the first and single point of communication for both registry participants and HCPs. The specialized staff, many of whom are obstetric nurses, have experience collecting data for observational studies from both patients and research naïve HCPs. They are experts at developing a rapport with HCPs and participants to facilitate data collection and build one-on-one relationships that will promote retention and reduce overall loss to follow up. To promote HCP engagement, status updates may be shared with HCPs through various means (i.e., email, newsletters, and the registry website). Materials provided will emphasize the mission of the registry to promote participant engagement and point participants to the website.

The registry will use streamlined data collection processes and simple, concise data collection forms that focus on specified outcomes to reduce the burden of reporting. The registry will provide multiple options for communication and data submission (e.g., phone, fax, mail, email,

website, web based/mobile application) and a flexible follow-up schedule to enhance retention and maximize data reporting. The registry will also attempt to collect contact information of family members or friends in case the participant cannot be reached, which can further promote retention. Finally, in countries where local guidelines permit, the registry will provide stipends to participants (at enrollment and at the end of data collection) and their HCPs who serve as data reporters (once all data have been collected and all queries have been resolved).

Assessment of Recruitment and Retention

Participant recruitment and retention are the greatest challenges experienced with pregnancy registries. Recruitment largely depends on a strong awareness campaign and product use or uptake in the market. It is important to note that low recruitment/enrollment in pregnancy registries may be due to limited use of the product, especially when the product is new to the market. Pregnancy registries typically enroll only a small fraction of all exposed pregnancies, regardless of awareness strategies employed.

To maximize recruitment and retention, the registry's recruitment and retention strategies will be flexible and will be continuously assessed. The registry will assess recruitment and retention by collecting information from reporters (i.e., HCPs and participating individuals) on the sources from which they received information about the registry (recruitment) and the reasons for which they ceased participation or were lost to follow-up (retention). Based on these assessments, the registry's recruitment and retention strategies will be adjusted to maximize registry participation. The registry's Scientific Advisory Committee (SAC) will also be consulted regarding recruitment and retention strategies.

9.6.4. Participant Registration

Pregnant individuals who are interested in providing data to the registry and participating in the registry may self-enroll through the web-based application or by calling the VRCC. To enroll, each individual will answer a series of screening questions to assess their eligibility, and, if eligible, they will be asked to provide informed consent, their primary contact information, alternate contact information for a family member or friend, contact information for HCPs who are/will be involved in their care or the care of their infant, and medical releases to allow these HCPs to provide data to the registry. To allow for full follow-up on all enrolled pregnant individuals and their infants prior to study end, the last participant will be enrolled on or before 31 December 2033.

9.6.5. Assessments for Safety

The registry is strictly observational; office visits and all treatment regimens will be determined by HCPs. No additional laboratory tests or HCP assessments will be required as part of this registry. Refer to Section 10 for reporting of adverse events (AEs) and other safety information.

9.7. Variables

9.7.1. Exposure Definitions and Ascertainment

Exposure to tirzepatide is a condition for inclusion into the exposed cohort. Exposure is defined as bodily uptake of any dose of tirzepatide at any time during pregnancy (from conception to pregnancy outcome) or prior to pregnancy (within a specified time based on the product's half-life). Due to the half-life of tirzepatide (approximately 5 days), tirzepatide is likely to be eliminated from the body within 5 half-lives (25 days or 3.5 weeks). Therefore, individuals exposed to tirzepatide within ≤25 days of DOC will be considered exposed. Individuals in the tirzepatide cohort who are exposed to other GLP-1 RA therapies during pregnancy or within 5 times the half-life of the drug prior to conception will be excluded from the main analysis to prevent class effect interactions. However, they may still be enrolled into the study as part of the tirzepatide exposed cohort.

Exposure to comparator products for weight management is defined as bodily uptake of any dose of a qualifying product for weight management at any time during pregnancy (from conception to pregnancy outcome) or prior to pregnancy (within 5-half-lives of DOC). Detailed information on drugs for weight management and their respective exposure windows are detailed in Drugs of Interest for Cohort Eligibility.

Detailed information on dose, route, frequency, dates/duration of exposure, and indication/reason for use will be collected, and exposure will be further categorized by earliest trimester of exposure. Section 9.7.5 provides information on the methods used to determine gestational age and trimester of exposure.

Exposure information will be updated at each pregnancy follow-up and changing exposures will be accounted for in the analysis. For example, if a pregnant individual was enrolled into the comparator cohort but later during pregnancy became exposed to tirzepatide, for the analysis they would be included in the tirzepatide exposed cohort.

9.7.2. Disease Definitions and Ascertainment

Being overweight with at least one weight-related comorbid condition or having obesity at the time of conception is a condition for inclusion into the main analysis cohorts, specifically, for comparison of the tirzepatide exposed cohort with the AOM unexposed comparator cohort. Disease information, including date of diagnosis, height, and weight (used to calculate BMI, where obesity is defined as BMI ≥30 kg/m^2 and overweight is defined as BMI ≥27 kg/m^2), will be collected at the time of enrollment into the study. History of maternal weight and weight-related comorbid conditions at the time of initial prescribing (if applicable), at the time of conception, at enrollment, during pregnancy, and near the time of delivery will be collected from HCPs.

9.7.3. Outcome Definitions and Ascertainment

Table 9.3 presents the definitions of the outcomes. For outcomes not simply reported by the HCP, additional information on outcome ascertainment is provided.

Table 9.3. Definitions of Outcomes

Outcome	Clinical Definition	Operational definition
Major congenital malformation (MCM)	An abnormality of body structure or function that is present at birth; is of prenatal origin (i.e., birth defect); has significant medical, social, or cosmetic consequences for the affected individual; and typically requires medical intervention[48]	The registry defines and codes MCMs with criteria specified by the CDC MACDP (Annex 3).[49] When participants who reside in Europe are enrolled, MCMs will also be defined and coded using the criteria specified by the EUROCAT[50] (Annex 3). Exclusion criteria for MCM analyses include exposure to known teratogens and/or investigational medications, and/or congenital infectious agents (e.g. zika, TORCH, HIV). To avoid misattribution of the malformation to the medication, MCMs not known to be associated with medication exposure, such as chromosomal abnormalities, genetic syndromes, fetal alcohol syndrome, prematurity-related conditions in infants born at <36 gestational weeks (e.g., patent ductus arteriosus, patent foramen ovale, inguinal hernias, or undescended testes), and positional effects (e.g., hip dislocation due to breech position or abnormal skull shape due to crowding by multiple fetuses), will not be considered MCMs in the statistical analyses.[51] Adjudication process: A panel of 2–3 independent experts in clinical genetics and neonatology, blinded to exposure, will review all malformations reported to the registry among live and non-live births and classify them using the CDC's MACDP system for US-reported cases (and EUROCAT, for EU-reported cases). Additionally, the birth defect evaluators will provide the organ system involved, etiology of the defect (e.g., chromosomal abnormality, prematurity), and approximate timing of the development of observed defects. If additional information is needed to aid in classification, the birth defect evaluators will request additional information using the targeted follow-up process outlined in Section 9.6.2. These assessments will be recorded in the study database. If there is a discrepancy, a third expert will independently review and code the case serving as tie breaker. These reviews will occur soon after the malformation is reported. Additional reviews will occur if new information is received for the case. The SAC that will not be blinded to exposure will assess the possible temporal association between exposure (to tirzepatide) and the development of observed defects. Additionally, the SAC will review all malformation cases reported to the registry and reach consensus on the coding of each case. The sponsor will not be involved in any activities related to case review or adjudication.

Outcome	Clinical Definition	Operational definition
Minor congenital malformation	An anomaly or abnormality of body structure that is present at birth, is of prenatal origin (i.e., birth defect), poses no significant health problem in the neonatal period, and tends to have limited social or cosmetic consequences for the affected individual[48]	The registry defines and codes minor congenital malformations with criteria specified as defined by the CDC.[52] The same process for adjudicating MCMs will be used to adjudicate minor congenital malformations.
Pre-eclampsia	A disorder of pregnancy associated with new-onset hypertension, which occurs most often after 20 weeks of gestation and frequently near term, and proteinuria. Or, in the absence of proteinuria, it is defined as new-onset hypertension with the new onset of any of the following: • Thrombocytopenia: platelet count less <100,000/mL • Renal insufficiency: serum creatinine concentrations >1.1mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease • Impaired liver function: elevated blood concentrations of liver transaminases to twice normal concentration • Pulmonary edema • New-onset headache unresponsive to medication and not accounted for by alternative diagnoses or visual symptoms[53,54]	As reported by HCP.
Eclampsia	New-onset tonic-clonic, focal, or multifocal seizures in the absence of other causative conditions such as epilepsy, cerebral arterial ischemia and infarction, intracranial hemorrhage, or drug use[53]	As reported by HCP.
Gestational diabetes	Any degree of glucose intolerance with onset or first recognition during pregnancy[55]	As reported by HCP.

Outcome	Clinical Definition	Operational definition
Pregnancy-induced hypertension	A disorder of pregnancy defined as a systolic blood pressure of 140 mmHg or more or a diastolic blood pressure of 90 mmHg or more, or both, on 2 occasions at least 4 hours apart after 20 weeks gestation, in a woman with a previously normal blood pressure[53,56]	As reported by HCP.
Maternal cardiac disease	Maternal cardiac disease will include but will not be limited to heart failure, coronary artery disease, pregnancy-associated myocardial infarction, cardiomyopathy, heart valve disorders	As reported by HCP.
Hyperemesis gravidarum	Uncontrolled vomiting requiring hospitalization, severe dehydration, muscle wasting, electrolyte imbalance, ketonuria, and weight loss of more than 5% of body weight[57]	As reported by HCP.
Inadequate gestational weight gain	Gestation weight gain that is below the recommended range at term based on pregnancy weight category	The registry will use the 2009 gestational weight gain guidelines of the Institute of Medicine[58] to determine inadequate maternal weight gain at term per maternal pre-pregnancy BMI category in singleton and twin gestations.
Spontaneous abortion (SAB)	An involuntary fetal loss or the expulsion of the products of conception occurring at <20 gestational weeks	Section 9.7.5 provides information on the methods used to calculate gestational age.
Stillbirth	As defined by the ACOG, an involuntary fetal loss occurring at ≥20 gestational weeks or, if gestational age is unknown, a fetus weighing ≥350 g[59]	Section 9.7.5 provides information on the methods used to calculate gestational age.
Induced abortion	An intervention that is intended to terminate a suspected or known ongoing intrauterine pregnancy and that does not result in a live birth[60]	As reported by HCP.
Preterm birth	A live birth occurring at <37 gestational weeks	Section 9.7.5 provides information on the methods used to calculate gestational age.

Outcome	Clinical Definition	Operational definition
Small for gestational age (SGA)	Birth weight <10th percentile for sex and gestational age using standard growth charts for full and preterm live-born infants[61]	For the determination of SGA, the registry will utilize the sex-specific international growth reference standards from the INTERGROWTH-21st for those born between $24^{0/7}$ and $42^{6/7}$ gestational weeks.[62,63] The INTERGROWTH-21st standards are the latest available global reference standards, representing contemporary information from an international, multi-ethnic, diverse population, and have been specifically developed for modern research.
Large for gestational age (LGA)	Birth weight >90th percentile for sex and gestational age using standard growth charts for full and preterm live born infants[64]	For the determination of LGA, the registry will utilize the sex-specific international growth reference standards from the INTERGROWTH-21st for those born between $24^{0/7}$ and $42^{6/7}$ gestational weeks.[62,63] The INTERGROWTH-21st standards are the latest available global reference standards, representing contemporary information from an international, multi-ethnic, diverse population, and have been specifically developed for modern research.
Rapid weight gain[65,66] (RWG)[a]	A positive change in the weight-for-age z-score greater than 0.67 between 2 different ages of childhood[67]	For the determination of rapid weight gain, the registry will utilize the sex-specific international growth reference standards from the WHO for children ages 0 to 59 months. The WHO growth standards are recommended for use in the US for infants and children 0 to 2 years of age.[57]
Postnatal growth deficiency[a]	Weight, length, or head circumference in $<10^{th}$ percentile for sex and age using standard growth charts	Postnatal growth deficiency will be evaluated at 4 and 12 months of infant age; deficiencies in weight, length, and head circumference will be evaluated separately. For the determination of postnatal growth deficiency, the registry will utilize the sex-specific international growth reference standards from the WHO for children ages 0 to 59 months. The WHO growth standards are recommended for use in the US for infants and children 0 to 2 years of age.[68]
Infant developmental delay[a]	Failure to achieve the developmental milestones for age, as defined by the CDC[69]	Infant developmental delay will be evaluated at 4 and 12 months of infant age for each CDC-defined category (social/emotional, language/communication, cognitive, and movement/physical development), separately.[b] HCPs will indicate on the data collection forms whether infants are meeting CDC-defined milestones (yes/no) for each category and age. Infants who are failing to achieve at least one milestone in any category will be considered developmentally delayed in that category.

Abbreviations: ACOG = American College of Obstetricians and Gynecologists; CDC = Centers for Disease Control and Prevention; EUROCAT = European Registration of Congenital Anomalies and Twins; HCP = healthcare provider; INTERGROWTH-21^{st} = International Fetal and Newborn Growth Consortium for the 21^{st} Century; LGA = large for gestational age; MACDP = Metropolitan Atlanta Congenital Defects Program; MCM = major congenital malformation; RWG = rapid weight gain; SAB = spontaneous abortion; SAC = Scientific Advisory Committee; SGA = small for gestational age; US = United States; WHO = World Health Organization

[a] Infants born preterm or SGA will be excluded from these calculations.
[b] Equivalent assessments are also accepted (e.g., Munich Functional Developmental Diagnostic- MFED or Bayley's Scale of Infant Development)

9.7.4. Potential Covariates and Confounders

In accordance with the FDA and Agency for Healthcare Research and Quality (AHRQ) guidance,[45,70] the following variables may be considered potential covariates and confounders, as appropriate:

- Geographic region
- Maternal age at conception
- Calendar year at conception
- Maternal race
- Maternal ethnicity
- Proxies for maternal socioeconomic status, including maternal education, employment status, and income
- Maternal pre-pregnancy BMI, calculated from pre-pregnancy weight and height
- Gestational age at registry enrollment
- Method of conception
- Number of fetuses
- Concurrent maternal medical conditions, including thyroid abnormalities, infectious diseases (including coronavirus disease 2019 [COVID-19]), asthma, diabetes, hypertension, seizure disorder, autoimmune diseases, depression and other psychiatric disorders, hepatitis, sexually transmitted diseases, and uterine or cervical abnormalities (e.g., congenital uterine abnormalities)
- Concurrent pregnancy-related maternal medical conditions or pregnancy complications, including pregnancy-induced hypertension, pre-eclampsia, eclampsia, gestational diabetes, preterm labor, placenta previa, placental abruption, incompetent cervix, ectopic pregnancy, molar pregnancy
- Number of previous pregnancies
- Previous pregnancy outcomes (SAB, stillbirth, induced abortion, live birth)
- Previous pregnancy complications
- Characteristics of previous live births (preterm, SGA, LGA)
- Previous fetus/infant with congenital malformations (major and minor)
- Family history of congenital malformations (major and minor)
- Disease characteristics, including duration, BMI, and weight-related comorbid conditions
- Maternal exposure to other drugs or biological products, including prescription and non-prescription drugs, dietary supplements (including folic acid and prenatal vitamins), and vaccines (including COVID-19), during pregnancy and gestational age at exposure
- Maternal exposure to tobacco, alcohol, marijuana, and recreational or illicit drugs during pregnancy and timing of exposure
- Maternal weight change prior to pregnancy
- Maternal weight change during pregnancy
- Labor type (induced vs. spontaneous)
- Delivery method and complications

Some variables may not be captured due to country-specific privacy regulations. Data collected at each study site will abide by regulatory guidelines, local privacy laws, and national provisions (e.g., date of birth and race/ethnicity will not be collected from participants in Germany). The collection of race and ethnicity data in the US will comply to the FDA guidance for industry, Collection of Race and Ethnicity Data in Clinical Trials and Clinical Studies for FDA-Regulated Medical Products.[47]

9.7.5. Other Variable Definitions and Ascertainment

Per the American College of Obstetricians and Gynecologists (ACOG), gestational age and the EDD should be determined by the obstetric HCP as soon as data are obtained regarding the last menstrual period (LMP), first accurate ultrasound, or both. The ACOG considers ultrasound measurement of the embryo or fetus in the first trimester (up to and including $13^{6/7}$ gestational weeks) the most accurate method to establish or confirm gestational age and discourages against changing the EDD based on subsequent ultrasounds. Any pregnancy without an ultrasound before $22^{0/7}$ gestational weeks to confirm or revise the EDD should be considered suboptimally dated. If the pregnancy resulted from assisted reproductive technology (ART), the obstetric HCP should use ART-derived gestational age (e.g., based on age of embryo and date of transfer) to determine EDD. The ACOG further recommends that the best estimate of EDD by the obstetric HCP, rather than estimates based on LMP alone, be used for research purposes.[71]

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

The registry will conform to the ACOG recommendations for determining the 'best' EDD, and EDD will be used to calculate gestational age. Based on the EDD, the following will be calculated:

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

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

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

DOC, defined as $2^{0/7}$ gestational weeks, will be calculated as first day of LMP plus 14 days (2 weeks).

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

Individuals will be considered exposed during pregnancy if the exposure occurs any time from 25 days prior to the DOC to the pregnancy outcome. For the analysis of MCM, first trimester exposure will be defined as exposure from 5 times the product's half-life (i.e., 25 days for tirzepatide) prior to the DOC to $13^{6/7}$ gestational weeks.

9.8. Data Sources

An overview of the data collection process and forms can be found in Section 9.6.

Registration Information

Collected from participant at enrollment

- Country of residence
- Date of first contact with registry
- Date of consent (enrollment)
- Recruitment source(s)
- Minimum data for assignment to a study cohort, including:
  - Pregnancy status
  - Diagnosis information
  - Exposure information
  - Prior enrollment status

Collected from HCP(s) – obstetric and prescriber, if needed, – at enrollment

- Minimum data for assignment to a study cohort, including:
  - Pregnancy status
  - Diagnosis information
  - Exposure information

Maternal Demographic Characteristics[1]

Collected from participant at enrollment

- Date of birth
- Country of residence
- Ethnicity
- Race
- Education
- Employment status
- Household income

[1] Data collected at each study site will abide by regulatory guidelines, local privacy laws, and national provisions (e.g., date of birth and race/ethnicity will not be collected from participants in Germany). The collection of race and ethnicity data in the US will comply to the FDA guidance for industry, Collection of Race and Ethnicity Data in Clinical Trials and Clinical Studies for FDA-Regulated Medical Products.

Maternal Pre-Pregnancy Anthropometrics

Collected from participant at enrollment

- Pre-pregnancy anthropometrics (weight and height) just prior to pregnancy, weight at approximately 12 months prior to pregnancy, and weight prior to starting prescription weight-loss medication if applicable (e.g., tirzepatide or other products for the treatment of overweight/obesity)

Collected from HCP at enrollment

- Pre-pregnancy anthropometrics (weight and height) just prior to pregnancy, weight at approximately 12 months prior to pregnancy, and weight prior to starting prescription weight-loss medication (e.g., tirzepatide)

Maternal Obstetrical History

Collected from obstetric HCP at enrollment; if not available from HCP, can be collected from participant

- Number of previous pregnancies, including multiple gestations
- Outcomes of previous pregnancies (SAB, stillbirth, induced abortion, live birth)
- Complications of previous pregnancies (e.g., pregnancy-induced hypertension, pre-eclampsia, eclampsia, gestational diabetes, preterm labor, placenta previa, placental abruption, incompetent cervix, ectopic pregnancy, molar pregnancy)
- Characteristics of previous live births (preterm, SGA, LGA)
- Number of previous fetuses/infants with congenital malformations (major and minor) and contributing factors
- Family history of congenital malformations

Collected from obstetric HCP at enrollment; if not available from HCP, can be collected from participant

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

Disease Information

Collected from HCP(s) – obstetric and prescriber, if needed – at enrollment

- Maternal history of diagnosis of overweight or obesity, including date of diagnosis
- Maternal pre-pregnancy anthropometrics (weight and height) just prior to pregnancy, weight 12 months prior to pregnancy, and additionally for tirzepatide-exposed participants, weight at the time of first tirzepatide prescription
- Weight-related comorbid conditions

Baseline Pregnancy Information

Collected from obstetric HCP at enrollment only

- First day of LMP

- Method of conception
- History of fertility treatment
- Relevant maternal and paternal risk factors (medical history and exposures) for adverse pregnancy outcomes (e.g., genetic disorders, consanguinity, occupation, past chemotherapy or exposure to teratogens)

Ongoing Pregnancy Information

Collected from obstetric HCP at enrollment, end of 2nd trimester, and pregnancy outcome; at the end of the 2nd trimester and pregnancy outcome, HCPs are asked only for updates to the data previously reported

- Number of fetuses
- EDD and method of determination (i.e., LMP, ultrasound, or ART data); if ultrasound-determined, timing of ultrasound (before $14^{0/7}$, before $22^{0/7}$, or at or after $22^{0/7}$ gestational weeks)
- Prenatal tests (e.g., ultrasound, amniocentesis, maternal serum alpha-fetoprotein, chorionic villus sampling) performed, including type of test (diagnostic or screening), date of test, and results/findings (e.g., congenital malformations)
- Relevant maternal medical conditions, including, but not limited to
  - Inheritable diseases
  - Thyroid abnormalities
  - Infectious diseases (e.g., COVID-19, toxoplasmosis, cytomegalovirus, rubella, parvovirus)
  - Asthma
  - Diabetes
  - Hypertension
  - Cardiac conditions (e.g., heart failure)
  - Seizure disorder
  - Autoimmune diseases
  - Anemia
  - Depression and other psychiatric disorders
  - Hepatitis
  - Sexually transmitted diseases
  - Uterine or cervical abnormalities, including congenital uterine abnormalities
- Concurrent pregnancy-related maternal medical conditions or pregnancy complications, including
  - Preterm labor
  - Placenta previa
  - Placental abruption
  - Incompetent cervix
  - Ectopic pregnancy
  - Molar pregnancy

Maternal Exposures during Pregnancy

Collected from HCP(s) – obstetric and prescriber, if needed – at enrollment, end of 2nd trimester, and pregnancy outcome; at the end of the 2nd trimester and pregnancy outcome, HCPs are asked only for updates to the data previously reported

- Exposure to tirzepatide, including indication/reason for use (approved according to label in country of residence), dose, route, frequency, and dates/duration of exposure, if available
- Exposure to other drugs or biological products (including prescription and non-prescription drugs, dietary/herbal supplements (including folic acid and prenatal vitamins), vaccines (including COVID-19), known teratogens (see Section 9.11.1.1.4), and investigational medications), including indication/reason for use, dose, route, frequency, and dates/duration of exposure, if available
- Exposure to tobacco, alcohol, marijuana, or recreational or illicit drugs, including timing of exposure, if available

Pregnancy Outcome Information

Collected from HCP(s) – obstetric and pediatric, if needed – at or after pregnancy outcome

- Pregnancy outcome (for each fetus, classified in one of the following mutually exclusive categories: SAB, stillbirth, induced abortion, and live birth)
- Maternal outcomes: pregnancy induced hypertension, pre-eclampsia, eclampsia, gestational diabetes, maternal cardiac disease, HG, and inadequate GWG.
- Date of pregnancy outcome
- Gestational age at pregnancy outcome
- Fetal/infant sex
- Fetal/infant weight, length, and head circumference at pregnancy outcome (when available)
- Labor type (spontaneous or induced)
- Route of delivery (i.e., vaginal delivery, assisted vaginal delivery, planned caesarean delivery, or emergency caesarean delivery)
- Delivery complications
- 5 Apgar scores
- Congenital malformations (major and minor), including post-mortem findings for fetal losses and assessment of potential contributing factors
- Maternal weight at (just prior to) pregnancy outcome
- For live births, prolonged hospitalization after delivery and reason
- For a non-induced fetal loss (SAB, stillbirth), factors that may have had an impact on the fetal loss and attribution
- For induced abortion, reason (e.g., finding on prenatal test, risk to mother's health, undesired pregnancy)

Infant Outcome Information

Collected from pediatric HCP at 4 and 12 months post-delivery

- Infant weight, length, and head circumference at birth (if not provided at pregnancy outcome) and at 4 and 12 months of age
- Achievement of the developmental milestones in each Centers for Disease Control and Prevention (CDC)-defined category (social/emotional, language/communication, cognitive, and movement/physical development) at 4 and 12 months of age
- Congenital malformations (major and minor) and assessment of potential contributing factors
- Infant death, including date and cause of death
- Infant illnesses (e.g., neonatal hypoglycemia), infections, and hospitalizations
- Breastfeeding information, including breastfeeding start/stop dates, maternal medicinal and recreational exposures during breastfeeding, and low milk supply

Targeted Follow-up Information

Collected from HCP(s) – obstetric and/or pediatric – at any time after pregnancy outcome

- Details of congenital malformations (major or minor) or other conditions
- Etiology
- Exposures that may have had an impact on the outcome
- Additional factors that may have had an impact on the outcome
- Specific questions requested by the sponsor and/or the birth defect evaluator

Data collection may be restricted in some cases due to country-specific privacy/data protection regulations.

Data Reconciliation

Although data may be collected from multiple reporters, a hierarchy will be applied during analysis that prioritizes the response from the reporter that is most likely to have the most accurate information on a per variable basis. For example, for disease characteristics and medicinal exposures, the primary position would go to information reported by the prescribing HCP, followed by the obstetric HCP, pediatric HCP, and the patient. Pregnancy information would have the obstetric HCP as the primary reporter, followed by the prescribing HCP, pediatric HCP, etc. Infant-related variables will have pediatric HCP as primary, followed by obstetric HCP, and prescribing HCP. Generally, HCP-reported information will always be used for all reporting, with two exceptions: patient-reported exposures may be used for initial cohort classification while HCP verification is pending and patient-reported LMP may be used for pregnancy dating if both the HCP-reported LMP and EDD are missing.

9.9. Study Size

9.9.1. Sample Size

Table 9.4 presents by outcome the sample size (number of live births or pregnant individuals, depending on the outcome) required in each cohort to detect a range of relative risks, from 1.5 to 5.5. Sample size calculations were performed with SAS® statistical software (version 9.4 or higher, SAS Institute, Cary, NC) for the outcomes using the Fisher's exact conditional test with Walters normal approximation method, and assuming a power of 80%, a 2-sided α level of 0.05, an equal number of individuals in each cohort (although other sampling ratios were considered), and observed prevalence of the outcomes in the comparator cohort equivalent to reference rates in the general population. These general population rates were obtained for most (but not all) of the outcomes from various sources, including the Metropolitan Atlanta Congenital Defects Program (MACDP), the National Vital Statistics System (NVSS), and published literature.

Although the registry aims to examine a variety of maternal, fetal, and infant outcomes, the target sample size for the registry is based on the primary outcome, overall prevalence of MCM, which also is the outcome with the most restrictive denominators and one of the lowest prevalence in the general population.

As shown in Table 9.4, 265 live births in the analysis population of each cohort are needed to detect a 3-fold increase in the overall prevalence of MCM between cohorts, or a relative risk of 3.

To estimate the number of pregnant individuals who will need to be enrolled to result in 265 live births per cohort, several factors were considered, including the expected registry live birth rate, the proportion of enrolled individuals expected to be exposed to tirzepatide in the first trimester, and the proportion of enrolled individuals expected to be excluded from the analysis population. It was assumed that 90% of enrolled individuals would be exposed in the first trimester, 90% of enrolled pregnancies would result in a live birth,[72,73] and 10% of enrolled individuals would be excluded from the analysis population due to the occurrence of pregnancy outcome prior to enrollment (retrospectively enrolled participants), exposure to a known teratogen or an investigational medication or congenital infectious agents during pregnancy (teratogen/investigational medication/congenital infectious agent-exposed participants), lack of pregnancy outcome data (participants lost to follow-up; assumed to constitute 5%), or inclusion of a prior pregnancy in the analysis population (subsequent pregnancies). These assumptions are based on experience with other similar study designs. To ensure adequate sample size in the main analysis population is achieved, enrollment of the main analysis population will be assessed throughout data collection. If higher than anticipated percentages of participants would be excluded from the analysis population, it will be assessed what (if any) potential mitigations should be implemented. It is also acknowledged that there could be some effective sample size loss due to the use of stabilized IPTW. The extent and potential mitigations for this will be assessed after approximately 100 participants have enrolled in each of the cohorts.

Given these assumptions, to attain 265 live births per cohort, 364 (=265/0.9/0.9/0.9) pregnant individuals would need to be enrolled in each of the three cohorts of the study population, and a

total of 1,092 individuals would need to be enrolled in the registry. This sample size will afford the study the ability to detect a 3-fold increase in the overall prevalence of the primary outcome, MCM, in the tirzepatide-exposed cohort, with meaningful confidence (95% confidence level). Additionally, Table 9.5 shows that, without any adjustments for multiple comparisons, the proposed sample size will also afford the study >80% power to detect a 3-fold increase in several of the secondary and exploratory outcomes.

The overall prevalence of MCM is higher among individuals with obesity (BMI >30 kg/m^2; 3.9%[26]) than that of the general population (3%).[74] However, because it is difficult to estimate the proportion of enrolled individuals who will have obesity at the time of conception (as some will have lost weight prior to conception due to weight management treatment), the more conservative approach assuming an overall prevalence of 3% has been chosen (i.e., the overall sample size calculations were based on the general population prevalence of MCM). Had the higher rate (3.9%) been used, the total sample size for the registry would have been substantially lower (828 vs. 1092). These assumptions also may be re-evaluated after interim analyses have been conducted.

Table 9.4. Sample Size Needed per Cohort to Detect Specific Relative Risk (Exposed: Tirzepatide Unexposed[c])

Outcomes[a]	Reference Prevalence in Unexposed Group	Reference	Denominator of Reference	RR= 1.5	RR= 2.0	RR= 2.5	RR= 3.0	RR= 3.5	RR= 4.0	RR= 4.5	RR= 5.0	RR= 5.5
Primary Objective												
MCM	3.0%	CDC 2008[74]	Live births	2,627	796	413	265	190	146	117	97	82
Secondary Objectives												
Pre-eclampsia	3.8%	Ananth 2013[75]	Pregnant individuals	2054	622	322	206	148	113	91	75	64
Eclampsia	0.281%	Butwick 2020[76]	Live births	28973	8824	4600	2961	2130	1640	1322	1101	940
Gestational diabetes	6.9%	Martin 2021[77]	Pregnant individuals	1161	350	180	115	82	62	50	41	35
Pregnancy-induced hypertension	6.5%	Butwick 2020[76]	Pregnant individuals	1088	327	169	107	76	58	46	38	32
SAB	11.8%	Wu 2019[78]	Pregnant individuals	596	177	90	57	40	30	24	19	16
Stillbirth	0.596%	MacDorman 2015[79]	Live births and stillbirths	13610	4142	2159	1389	999	769	619	516	440
Induced abortion	18.6%	Jatlaoui 2019[80]	Live births	343	100	50	31	21	15	12	9	NA[b]
Preterm birth	8.47%	Martin 2021[77]	Singleton live births	868	260	134	85	60	46	36	30	25
SGA	10.0%	By definition	Live births	721	215	110	70	49	37	29	24	20
Postnatal growth deficiency	10.0%	By definition	Live births	721	215	110	70	49	37	29	24	20
Infant developmental delay	13%	Rosenberg 2008[81]	Live births	532	158	80	50	35	26	71	17	14
Exploratory Objectives												
Heart Failure	0.12%	Mogos 2018[82]	Pregnant individuals	667975	20706	10798	6952	5002	3853	3107	2588	2210

Outcomes[a]	Reference Prevalence in Unexposed Group	Reference	Denominator of Reference	RR= 1.5	RR= 2.0	RR= 2.5	RR= 3.0	RR= 3.5	RR= 4.0	RR= 4.5	RR= 5.0	RR= 5.5
Peripartum Cardiomyopathy	0.03%	Harper 2012[83]	Live births	272189	82925	43251	27847	20039	15437	12450	10374	8858
Hyperemesis gravidarum	2.5% (0.3 to 3.5%)	ACOG 2015[84]	Pregnant individuals	3171	962	500	321	230	176	142	118	100
Inadequate GWG	15% (12 to 25%)	CDC 2015[85]	Pregnant individuals	448	132	67	42	29	22	17	13	11
LGA	10.0%	Hocquette 2021[86]	Live births	721	215	110	70	49	37	29	24	20
Rapid infant weight gain	8% (5 to 14%)	Eckhardt 2016[87]	Live births	925	278	143	91	64	49	39	32	27

Abbreviations: GWG = gestational weight gain; MCM = major congenital malformation; NA = not available; reference prevalence = prevalence of outcome in general population for pregnant individuals of any age; RR = relative risk; SAB = spontaneous abortion; SGA = small for gestational age.

[a] Only outcomes with published reference rates in the general population are included in the table.

[b] For induced abortion, an RR of 5.5 with a reference rate of 18.6% in the unexposed cohort would result in a rate above 100% in the exposed cohort.

[c] Sampling ratio is 1:1 (Exposed: Tirzepatide Unexposed). Comparisons between tirzepatide exposed vs. AOM active comparator and tirzepatide exposed vs. AOM unexposed comparator will be conducted separately.

Notes: Sample size calculations were performed in SAS (version 9.4) for the outcomes using Fisher's exact conditional test with Walters normal approximation method, and assuming a power of 80% and a 2-sided α level of 0.05.

Table 9.5. Power to Detect a 3-fold Increase, by Study Outcome

Outcomes	Power Estimate
MCM	80%
Pregnancy-induced hypertension	>80%
Pre-eclampsia	>80%
Eclampsia	5.9%
Gestational diabetes	>80%
Heart failure	0%
Peripartum Cardiomyopathy	0%
Hyperemesis gravidarum	71.5%
Inadequate maternal weight gain	>80%
SAB	>80%
Stillbirth	21.4%
Induced abortion	>80%
Preterm birth	>80%
SGA	>80%
LGA	>80%
Postnatal growth deficiency	>80%
Rapid infant weight gain	>80%
Infant developmental delay	>80%

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

Notes: No adjustments for multiple comparisons were made. References for rates are presented in Table 9.4.

9.9.2. Assessment of Study Feasibility

To assess the feasibility of this study, data-based assumptions regarding the prevalence of obesity, pregnancy, and tirzepatide uptake were made to estimate the number of individuals who will potentially be exposed to tirzepatide during pregnancy. The prevalence of obesity among individuals in the US, Germany, and the UK was assumed to be 39.7%, 28.8%, and 27.2%, respectively,[88-90] and the proportion receiving pharmacotherapy for obesity was assumed to be 0.8%.[91] It was further assumed that 15% of those receiving pharmacotherapy for obesity would be treated with tirzepatide. These assumptions were applied to the population of females of childbearing potential (aged 15–49 years) in the US, Germany, and UK (approximately 74.4 million, 42.7 million, and 14.7 million, respectively), which yielded an estimated 54,641 individuals of childbearing potential who will potentially receive tirzepatide. After application of the live birth rates (average annual number of births during a year per 1,000 persons in the population; US: 12.33/1000; Germany: 9.00/1000; UK: 8.05/1000[92]) and the rate of pharmacotherapy discontinuation during pregnancy among individuals with obesity (95% assumed rate of discontinuation due to contraindication during pregnancy), it was estimated that 305 individuals in the US, UK, and Germany may potentially be exposed to tirzepatide during pregnancy over a 10-year period.

This estimate is less than the target sample size for the exposed cohort (364 enrolled individuals); however, this is considered a conservative estimate for several reasons. First, it is anticipated that the proportion of individuals exposed to tirzepatide will increase over the

duration of the study. Furthermore, the feasibility calculations were based on the prevalence of obesity alone, since reliable statistics regarding the prevalence of overweight and weight-related comorbidities are not available. Therefore, the estimated number of individuals with the indication could be an underestimate. Registry enrollment will be monitored, and further expansion to include additional countries will be considered as needed.

Sponsor will make best efforts to achieve its target sample size through various awareness campaign efforts (see Section 9.6.3). However, lack of motivation to participate in pregnancy registries could result in limited registry enrollment and challenges in meeting scientific objectives. To assess feasibility as outlined in the FDA Postapproval Pregnancy Safety Studies Guidance for Industry,[45] an ongoing review of registry enrollment, real world drug utilization, spontaneous pregnancy exposure reports to the company pharmacovigilance database, and external pregnancy registry publications will be performed. In conjunction with this effort, registry recruitment and awareness strategies will be evaluated to ensure that recruitment efforts reflect the size of the potential study population. If the assessment suggests that collecting sufficient information to address study objectives is infeasible, Lilly will submit a proposal to terminate additional recruitment into the pregnancy exposure registry, as a prospective registry would not be warranted.[45] If this proposal to terminate additional recruitment is submitted, follow-up will continue for the individuals already enrolled. Uptake monitoring will also continue in a US administrative claims database.

9.10. Data Management

Participant data are recorded on data forms. Investigators and study personnel at the VRCC) are responsible for the integrity of the data (i.e., accuracy, completeness, legibility, and timeliness) reported to the sponsor.

Paper/electronic data collection forms will be used to capture study-specific participant data. Instructions for completion and correction of data collection forms will be provided.

Appropriate measures such as encryption or deletion must be enforced to protect the identity of participants when transmitting data, in all presentations and publications as required by local/regional/national requirements.

For electronic case report forms: The system for electronic data capture (EDC) and support services will be Medidata Rave.

An audit trail will be maintained in the EDC application containing as a minimum: identification of the person entering the data, date and time of the entry and reason for the correction, the original entry, and the corrected entry.

To enable evaluations and/or audits from regulatory authorities or the study sponsor, the investigator agrees to keep records, including the identity of all participating patients, all original signed consent to release information, copies of all electronic case report forms (eCRFs), serious adverse event (SAE) forms, source documents, and adequate documentation of relevant correspondence. The records should be retained by the investigator according to local regulations or as specified in the study-specific site contract, whichever is longer.

9.11. Data Analysis

Analyses will be conducted by PPD in accordance with the study objectives, statistical analysis plan (SAP), table/listing shells, and applicable guidelines. Data analyses will be performed with SAS® statistical software (version 9.4 or higher, SAS Institute, Cary, NC). Additional details will be provided in the SAP.

To minimize the potential impact of bias, adjusted analyses (Section 9.11.2.4), stratified analyses (Section 9.11.2.5), supplementary analyses (Section 9.11.2.6), and sensitivity analyses (Section 9.11.2.7) will be performed.

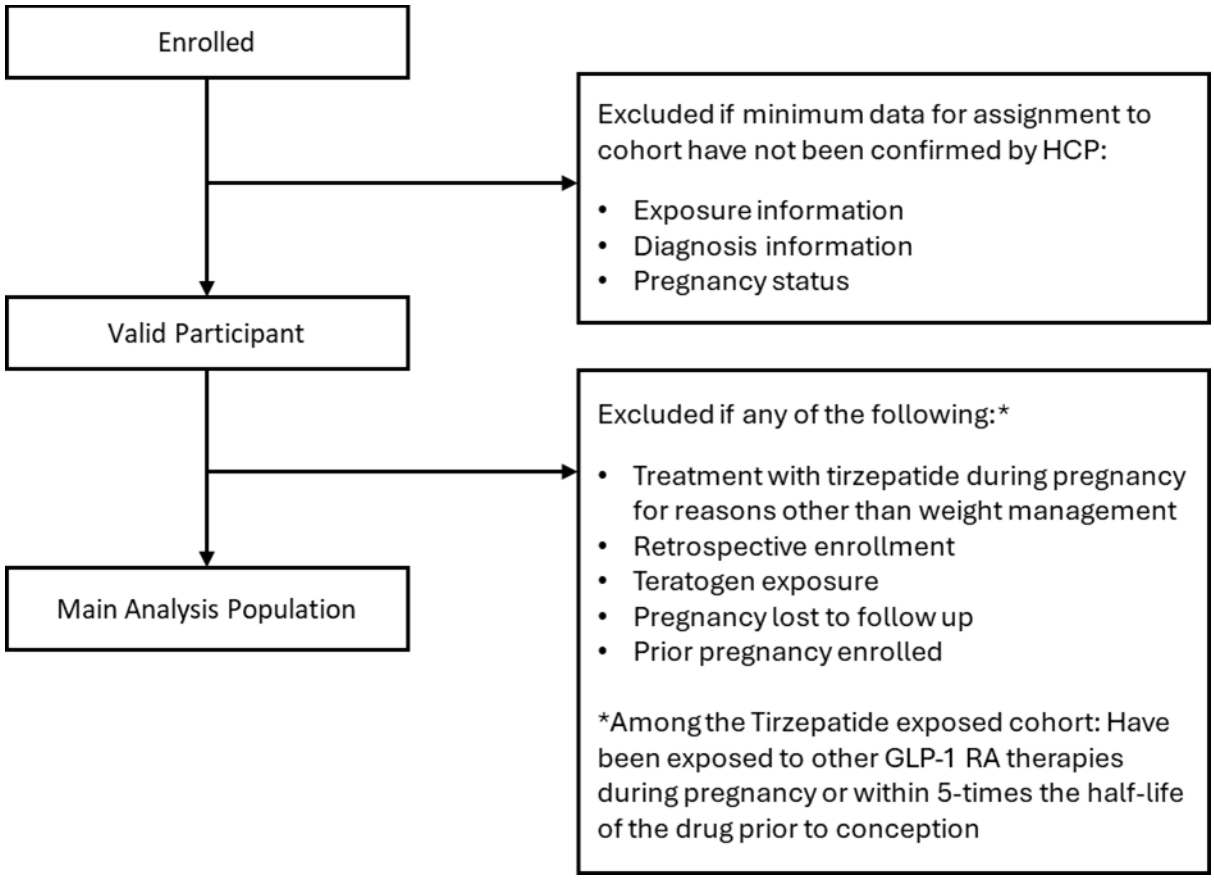
9.11.1. Definition of Analysis Sets

9.11.1.1. Analysis Population

As depicted in Figure 9.2, the main analysis population will include participants who:

- Are valid (Section 9.11.1.1.1)
- Had a qualifying diagnosis at the time of prescribing (Section 9.11.1.1.2)
- Are prospectively enrolled (Section 9.11.1.1.3)
- Are not exposed to teratogens or investigational medications or congenital infectious agents during pregnancy (Section 9.11.1.1.4)
- Are not considered lost to follow-up (Section 9.11.1.1.5)
- Are not already included in the analysis population for a prior pregnancy (Section 9.11.1.1.6), and
- Among the tirzepatide exposed cohort, have not been exposed to other GLP-1 RA therapies during pregnancy or within 5 times the half-life of the drug prior to conception.

For the analyses of preterm birth, SGA, postnatal growth deficiency, rapid infant weight gain, and infant developmental delay, multiple gestation pregnancies will be excluded from the analysis population.



Abbreviation: HCP = healthcare professional; GLP-1 RA = glucagon-like peptide-1 receptor agonist.

Figure 9.2. Attrition diagram.

9.11.1.1.1. Valid Versus Invalid Participants

A valid participant is defined as a pregnant individual with sufficient data, submitted or confirmed by an HCP, for determining inclusion/exclusion into one of the study population cohorts (Section 9.5.2). Participants who lack the minimum data required for determining inclusion/exclusion into one of the study cohorts or who lack confirmation from an HCP will be considered invalid. Invalid participants will be enumerated in each registry report but will not be included in statistical analyses.

9.11.1.1.2. Treatment with Tirzepatide during Pregnancy for Indications Other Than Weight Management

The focus of the current study is limited to exposures to tirzepatide prescribed for the treatment of obesity or overweight with at least one weight-related comorbid condition. Therefore, individuals prescribed tirzepatide for indications other than weight management (e.g., type 2 diabetes) can be enrolled into the current study, but they will be excluded from the main analysis population. The main analysis population will only include participants treated for obesity or overweight with at least 1 weight-related comorbid condition. Individuals meeting the criteria for

enrollment who also have comorbid type 2 diabetes are eligible for inclusion in the main analysis population.

9.11.1.1.3. Prospectively Enrolled Versus Retrospectively Enrolled Participants

The registry will encourage prospective registration; however, retrospective enrollment in the registry will be permitted. A prospectively enrolled participant is defined as a pregnant individual who enrolls or makes initial contact with the registry prior to pregnancy outcome. A retrospectively enrolled participant is defined as a pregnant individual who enrolls or makes initial contact with the registry after the pregnancy outcome (e.g., live birth, stillbirth, SAB, induced abortion) has occurred (up to 12-months after pregnancy outcome).

Retrospectively enrolled participants can introduce bias toward the reporting of more unusual and severe outcomes and are less likely to be representative of the general population than prospectively enrolled participants. Therefore, retrospectively enrolled participants will be excluded from the main analysis population but will be included in supplementary analyses.

Diagnostic prenatal tests (e.g., ultrasound to scan for structural defects at approximately 20 gestational weeks, chorionic villus sampling, and amniocentesis) can determine with high accuracy whether a fetus has a structural or chromosomal abnormality. Therefore, inclusion of individuals who have had diagnostic prenatal testing in the analysis population may introduce bias. To examine this potential bias, a sensitivity analysis that applies a stricter definition of prospective enrollment will be conducted. For this analysis, individuals who enroll or make initial contact with the registry prior to diagnostic prenatal testing (and pregnancy outcome) will be considered prospectively enrolled, and individuals who enroll or make initial contact with the registry after diagnostic prenatal testing, regardless of the results, will be considered retrospectively enrolled in addition to individuals who enroll after pregnancy outcome. In this sensitivity analysis, the outcomes of individuals who enroll prior to diagnostic prenatal testing will be compared with those of individuals who enrolled after diagnostic prenatal testing.

9.11.1.1.4. Participants Exposed to Teratogens or Investigational Medications

Participants will be considered exposed to teratogens or investigational medications during pregnancy if a dose is taken at any time during pregnancy (from conception to pregnancy outcome) or prior to pregnancy (within a specified time period based on the product's half-life). If the teratogen or investigational medication has a relatively short half-life (<3 days), participants will be considered exposed during pregnancy if a dose is taken during the period of time just prior to conception, between the first day of the LMP and the DOC. If the teratogen or investigational medication has a longer half-life, participants will be considered exposed during pregnancy if a dose is taken prior to conception within a period equivalent to 5 times the product's half-life. A list of teratogens has been developed and will be continually updated based on the data available in the Teratogen Information System (TERIS) database of teratogenic agents and recent publications.[93-96] Participants exposed to teratogens or investigational medications during pregnancy will be excluded from the main analysis population but will be included in supplementary analyses.

9.11.1.1.5. Participants Lost to Follow-up

A participant will be considered lost to follow-up if follow-up information is never obtained or is unavailable; pregnant individuals without pregnancy outcome information will be considered lost to follow-up for pregnancy outcome, and live-born infants without follow-up data after birth will be considered lost to follow-up. Lost to follow-up is considered by outcome and participants are eligible to be included in calculation of all outcomes they contributed to up to the point of loss to follow-up (e.g., if pregnancy complications were observed prior to a maternal death, any observed complications as well as the pregnancy outcome would be captured and included in analyses, but after that point the case would be considered lost to further follow-up). Section 9.6.1 provides more information on the circumstances under which participants will be considered lost to follow-up. Information from these participants (e.g., baseline characteristics, abnormal prenatal test results, and reason for loss to follow-up, if available) will be summarized in each registry report, but these participants will be excluded from the main analysis population.

9.11.1.1.6. Subsequent Pregnancies

Individuals who have previously enrolled in the registry with a prior pregnancy will be eligible to enroll in the registry, but any subsequent pregnancy will be excluded from the main analysis population if a prior pregnancy is included. Subsequent pregnancies will be included in supplementary analyses.

9.11.1.1.7. Multiple Gestation Pregnancies

Multiple gestation pregnancies will be enrolled in the registry and included in the main analysis population; however, for the analyses of preterm birth, SGA, LGA, rapid infant weight gain, postnatal growth deficiency, and infant developmental delay, multiple gestation pregnancies will be excluded from the main analysis population due to the higher risk of these outcomes in twins and higher order multiples.

9.11.2. Statistical Methods

Registry data will be summarized in tables and listings by study cohort, as appropriate. These data include maternal demographic characteristics and pre-pregnancy anthropometrics, pregnancy information, maternal obstetrical history, family history of congenital malformations, disease information, maternal exposures during pregnancy, pregnancy outcome information (including gestational age of outcome), and infant outcome information.

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

Pair-wise comparisons of demographic and baseline characteristics and event rates of the outcomes of interest will be conducted between the study cohorts, as follows:

- Comparison #1: Tirzepatide exposed cohort vs. AOM active comparator cohort

- Comparison #2: Tirzepatide exposed cohort* vs. AOM unexposed comparator cohort
  *Comparison #2 will include a subset of tirzepatide exposed cohort who have obesity or are overweight with at least one weight-related comorbid condition at the time of conception so as to improve comparability to AOM unexposed comparator cohort with the same obesity-related eligibility criteria.

For the analysis, participants from all countries will be pooled. Comparisons will be conducted using the methods described below, and p-values and 95% confidence intervals will be reported, as appropriate, to reflect statistical uncertainty. All outcomes will be analyzed as binary variables. The study is not powered for multiple comparisons; thus, p-values associated with secondary or exploratory outcomes will be nominal.

In addition, the prevalence of the outcomes in the general population and/or populations of individuals overweight or with obesity, from the literature, will be used to put the registry-observed outcome prevalences into context.

9.11.2.1. Analysis of Primary Outcome

Prevalence of the primary outcome will be calculated according to the conventions described in Table 9.6. In general, prevalence will be calculated by dividing the number of cases with an MCM by the appropriate denominator. Prevalence is preferred over incidence when examining pregnancy outcomes, such as congenital malformations, because incidence cannot be reliably estimated given the complexities in the reproductive process.[97]

For MCM, prevalence in the exposed cohort will be calculated among the subset of individuals who are exposed during the first trimester. For the primary analysis, prevalence will be calculated among live births, and a secondary analysis will be conducted among live births and fetal losses (Table 9.6).

The unweighted univariate regression will be used to compare the crude (unadjusted) relative risks (RRs) of MCM in the tirzepatide exposed and each of the comparator groups, respectively: tirzepatide exposed vs. AOM active comparator and tirzepatide exposed vs. AOM unexposed comparator.

Adjusted methods will incorporate weights estimated using the inverse probability of treatment weighting (IPTW) method to balance the cohorts regarding observable covariates. A weighted generalized linear model using a binomial family and a log (RR) link with robust sandwich variance estimation or a modified Poisson regression[98] with robust error variance will be employed to estimate an adjusted RR. As with the unweighted analysis, two sets of comparisons will be conducted separately: tirzepatide vs. AOM active comparator and tirzepatide vs. AOM unexposed comparator.

The adjusted comparison of the overall prevalence of MCM observed in the tirzepatide exposed and the comparator cohorts will be considered the primary analysis. A p-value <0.05 will be considered statistically significant.

Table 9.6. Calculation of Primary Outcome Prevalence

Outcome	Numerator	Denominator
Primary analysis: among live births	Live births with confirmed (by adjudication) MCMs (excluding MCMs not known to be associated with medication exposure[a]) among individuals with pregnancy outcome data and, if applicable, exposure during 1st trimester	Live births among individuals with pregnancy outcome data and, if applicable,[b] exposure during 1st trimester
Secondary analysis: among all pregnancy outcomes	Live births and fetal losses[c] with confirmed (by adjudication) MCMs (excluding MCMs not known to be associated with medication exposure[a]) among individuals with pregnancy outcome data and, if applicable, exposure during 1st trimester	Live births and fetal losses[c] among individuals with pregnancy outcome data and, if applicable, exposure during 1st trimester

Abbreviation: MCM = major congenital malformation.

[a] To avoid misattribution of the malformation to the medication, MCMs not known to be associated with medication exposure such as chromosomal abnormalities, genetic syndromes, fetal alcohol syndrome, prematurity-related conditions in infants born at <36 gestational weeks (e.g., patent ductus arteriosus, patent foramen ovale, inguinal hernias, or undescended testes), and positional effects (e.g., hip dislocation due to breech position or abnormal skull shape due to crowding by multiple fetuses) will not be considered MCMs in the statistical analyses comparing MCM prevalence between the cohorts.[51]

[b] Exposure during first trimester applicable only for exposed cohorts.

[c] Fetal losses include stillbirths, SABs, and induced abortions.

9.11.2.2. Analysis of Secondary and Exploratory Outcomes

Prevalence of the secondary and exploratory outcomes will be calculated according to the conventions described in Table 9.7. In general, the prevalence of each outcome will be calculated by dividing the number of cases of the outcome by the appropriate denominator for that particular outcome, based on clinical knowledge.

Table 9.7. Calculation of Secondary and Exploratory Outcome Prevalence

Outcome [Exposure window]	Numerator	Denominator
Secondary outcomes		
Maternal pregnancy complications		
Gestational diabetes [Exposure: Any trimester]	Individuals with gestational diabetes	Individuals included in the analysis population
Sensitivity analysis: Gestational diabetes	Gestational diabetes among pregnancies with pregnancy outcome data	Individuals with pregnancy outcome data
Pregnancy-induced hypertension [Exposure: Any trimester]	Individuals with pregnancy-induced hypertension	Individuals with pregnancy of 20 gestational weeks or more
Sensitivity analysis: Pregnancy-induced hypertension	Pregnancy-induced hypertension among pregnancies with pregnancy outcome data	Individuals with pregnancy of 20 gestational weeks or more with pregnancy outcome data
Pre-eclampsia [Exposure: Any trimester]	Individuals with pre-eclampsia	Individuals with pregnancy of 20 gestational weeks or more
Sensitivity analysis: Pre-eclampsia	Pre-eclampsia among individuals with pregnancy outcome data	Individuals with pregnancy of 20 gestational weeks or more and with pregnancy outcome data
Eclampsia [Exposure: Any trimester]	Individuals with eclampsia	Individuals with pregnancy of 20 gestational weeks or more
Sensitivity analysis: Eclampsia	Eclampsia among individuals with pregnancy outcome data	Individuals with pregnancy of 20 gestational weeks or more with pregnancy outcome data
Fetal Outcomes		
SAB [Exposure: DOC to $\leq 19^{6/7}$ gestational weeks]	SABs among individuals with pregnancy outcome data who are enrolled (and exposed, if applicable) prior to 20 gestational weeks	Individuals with pregnancy outcome data who are enrolled (and exposed, if applicable) prior to 20 gestational weeks
Induced abortion [Exposure: Any trimester]	Individuals with pregnancy ending in induced abortions	Individuals included in the analysis population
Sensitivity analysis: Induced abortion	Induced abortions among individuals with pregnancy outcome data	Individuals with pregnancy outcome data
Stillbirth [Exposure: Any trimester]	Individuals with pregnancy ending in stillbirth	Individuals included in the analysis population
Sensitivity analysis: Stillbirth	Stillbirths among individuals with pregnancy outcome data	Individuals with pregnancy outcome data
Infant Outcomes		
Minor congenital malformations [Exposure: Any Trimester]	Live births with minor congenital malformations among individuals with pregnancy outcome data	Live births among individuals with pregnancy outcome data
Preterm birth [Exposure: DOC to <37 weeks gestation]	Singleton preterm live births without MCMs among individuals with pregnancy outcome data who are enrolled (and exposed, if applicable) prior to 37 gestational weeks	Singleton live births without MCMs among individuals with pregnancy outcome data who are enrolled (and exposed, if applicable) prior to 37 gestational weeks

Outcome [Exposure window]	**Numerator**	**Denominator**
SGA [Exposure: Any trimester]	Singleton live births who are SGA at birth among individuals with pregnancy outcome data	Singleton live births among individuals with pregnancy outcome data
Sensitivity analysis: SGA	Singleton live births without MCMs who are SGA at birth among individuals with pregnancy outcome data	Singleton live births without MCMs with weight data among individuals with pregnancy outcome data
Postnatal growth and development outcomes		
Postnatal growth deficiency (at 4 and 12 months) [Exposure: Any trimester]	Singleton infants with postnatal growth deficiency based on weight/length/head circumference among infants with weight/length/head circumference data at the time point	Singleton infants with follow-up data at the time point
Sensitivity analysis: Postnatal growth deficiency (at 4 and 12 months)	Singleton infants without MCMs who were not born preterm or SGA with postnatal growth deficiency based on weight/length/head circumference among infants with weight/length/head circumference data at the time point	Singleton infants without MCMs who were not born preterm or SGA with weight/length/head circumference data at the time point
Infant developmental delay (at 4 and 12 months) [Exposure: Any trimester]	Singleton infants with developmental delay in a particular category among infants with developmental milestone data for the category at the time point	Singleton infants with follow-up data at the time point
Sensitivity analysis: Infant developmental delay (at 4 and 12 months)	Singleton infants without MCMs who were not born preterm or SGA with developmental delay in a particular category among infants with developmental milestone data for the category at the time point	Singleton infants without MCMs who were not born preterm or SGA with developmental milestone data for the category at the time point
Exploratory outcomes		
Hyperemesis gravidarum [Exposure: Any trimester]	Hyperemesis gravidarum	Individuals included in the analysis population
Inadequate gestational weight gain [Exposure: Any trimester]	Inadequate gestational weight gain	Individuals included in the analysis population
Maternal cardiac disease [Exposure: Any trimester]	Cardiac disease	Individuals included in the analysis population
LGA [Exposure: Any trimester]	Singleton live births at birth who were born LGA among individuals with pregnancy outcome data	Singleton live births among individuals with pregnancy outcome data
Rapid infant weight gain [Exposure: Any trimester]	Singleton live births without MCM who were not born preterm or SGA with rapid weight gain among infants with at least two recorded weight measurements	Singleton infants without MCMs who were not born preterm or SGA with at least two recorded weight measurements

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

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

- For live birth and infant outcomes (i.e., preterm birth, SGA, LGA, postnatal growth deficiency, rapid infant weight gain, and infant developmental delay), prevalence will be calculated among live births/infants excluding MCMs and multiple gestation pregnancies due to the higher risk of these outcomes among infants in these groups.
- For postnatal growth deficiency, rapid infant weight gain, and infant developmental delay infants born preterm, or SGA will be excluded from the main analysis population (denominator) due to different growth trajectories.
- For SAB and preterm birth, prevalence will be calculated among the subset of individuals who are enrolled in the registry prior to 20 and 37 gestational weeks, respectively. Additionally, for these time-to-event outcomes, data will be censored at appropriate time points: 20 gestational weeks for SAB and 37 gestational weeks for preterm birth.
- For pregnancy complications prevalence will be calculated according to the following assessment windows:
    - Pregnancy induced hypertension reported for the first time among participants after 20 weeks gestation.
    - Pre-eclampsia/eclampsia reported among participants after 20 weeks of gestation.
    - New-onset gestational diabetes reported among participants at any time during pregnancy
    - Inadequate maternal weight gain reported among participants at any time during pregnancy.
    - HG reported among participants anytime during pregnancy.
- Prevalence will be calculated at multiple time points for postnatal growth deficiency, rapid infant weight gain, and infant developmental delay will be assessed at 4 months (±2 weeks) and 12 months (±2 weeks) of infant age. At each time point, prevalence will be calculated among infants with data available for the particular outcome at that time point. If there is no assessment available at 4 and/or 12 months, available data will be evaluated based on the actual time of assessment (e.g., if the infant was measured at 6 months, these data will be compared to the values appropriate for a 6-month-old infant based on the growth charts). However, only development at 4 and 12 months will be reported as study outcomes, results from other time points will be reported in a separate category.

The unweighted univariate regression will be used to compare the crude (unadjusted) RRs for all outcomes. Adjusted methods will incorporate weights estimated using the IPTW method to balance the cohorts with regard to observable covariates (Section 9.11.2.4). A weighted generalized linear model using a binomial family and a log (relative risk) link will be employed to estimate an adjusted relative risk.

9.11.2.3. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized with descriptive statistics, and balance between cohorts will be assessed using standardized differences. These data will be presented before and after balancing using the IPTW method (Section 9.11.2.4). In addition, within each cohort, those included in the main analysis population will be compared with those excluded from the main analysis population for being lost to follow-up, retrospectively enrolled, exposed to teratogens or investigational medications during pregnancy, or having already been included in the analysis population for a prior pregnancy.

9.11.2.4. Adjustment for Covariates and Confounders

Because of the real-world nature of the study, there is a high potential for imbalance between the cohorts regarding observed covariates. To address this imbalance, adjusted analyses that employ the IPTW method will be conducted in each of the two comparison sets separately: tirzepatide exposed vs. AOM active comparator and tirzepatide exposed vs. AOM unexposed comparator. The IPTW method is widely used in observational studies to adjust for confounding due to differences between comparator groups that arise in observational data.[99-101]

The IPTW allows us to estimate an average treatment effect, which is interpreted as the effect of treatment in the entire study population.[102]

The IPTW approach assigns a weight to each participant based on observed demographical and clinical covariates:

- For the tirzepatide cohort, the weight is equivalent to the inverse of the propensity score (PS; i.e., the probability of the participant belonging in their assigned cohort).
- For each of the comparator cohorts, the weight is equivalent to the inverse of 1 minus the PS.

PS, the probability of treatment assignment conditional on observed baseline characteristics, will be derived with logistic regression. There is a large number of potential confounders, as described in Section 9.7.4. To ensure key clinical variables are included in the PS estimation, a set of covariates to be included in the PS model will be prespecified in the SAP, based on causal diagrams along with the literature and clinical expertise. Examples of such variables are age and pregnancy history. These variables will be included in the PS model even if balanced between the treatment cohorts due to their significance as risk factors for the outcome of interest. Other variables will be inspected for balance between the treatment cohorts before and after applying the IPTW. Covariates that remain imbalanced between the treatment cohorts will be added in the PS model, and balance between the treatment cohorts will be re-inspected. Any covariates that continue to show imbalance may be added to the final outcome model for regression adjustment. The PS estimation and assessment of covariate balance will be conducted without examining the study outcomes.

This method can occasionally generate extremely large weights for a small number of participants, creating unstable results that are highly dependent on a small number of participants. To address this issue, stabilized weights will be used. Stabilized weights for each

treatment cohort are created by multiplying the weight of the respective treatment cohort (i.e., 1/PS for the tirzepatide cohort and 1/[1−PS] for the comparator cohort) by the marginal probability of receiving the treatment in the respective treatment cohort. Distribution of stabilized weights will be inspected with the summary statistics (mean, standard deviation, minimum, and maximum) and histograms to ensure there are no extreme weights. To reduce the influence of extreme weights, the stabilized weights will be truncated at the first and 99th percentiles. A sensitivity analysis will use trimming to assess any impact of excluding extreme weights.

Once the PSs are estimated, we will assess the PS distribution of each treatment group for the imbalance between two cohorts (the extent of their overlap) and the presence of extreme PSs. If after applying stabilized weights, the cohorts remain unbalanced, other methods may be considered, such as revising the PS model by including interaction or non-linear quadratic terms, using overlapping weights (e.g., if the positivity assumption is being violated), or further adjustment in the regression model for the unbalanced baseline characteristics. Overlapping weights emphasize the target population with the most overlap in observed characteristics between treatments, by continuously down-weighting the units in the tails of the PS distribution.[103]

The weights will be incorporated into the regression model (aka weighted regression) for estimating adjusted RR; covariates that remain not well-balanced after the final set of weights are created (defined as having an absolute standardized difference of greater than 10% after weighting) will be further adjusted for through inclusion into the regression model as a covariate. In addition, a high proportion of missing data for a covariate could make application of the IPTW method more challenging, as weights can be estimated only for participants with known values. If there is a high degree of missingness among clinically important covariate data, multiple imputation of these variables will be considered where the variables are assumed missing at random. Variables whose missingness would trigger additional sensitivity analyses with imputation will be indicated in the SAP. For the imputation, Rubin's rules will be applied, and the imputed values will be used for weight estimation by estimating the treatment effect for each imputed dataset and then averaging them into a single treatment effect estimate.[104,105] Further details on this will be provided in the SAP.

It is also acknowledged that IPTW procedure could result in loss of effective sample size compared to the actual (apparent) sample size if the overlap between tirzepatide exposed cohort and the comparator cohorts is small. Once sufficient data have become available (approximately 100 patients per cohort), the PS distributions will be assessed to determine whether there is sufficient overlap between the cohorts (the 2 treatment comparisons treated separately) to achieve the desired power in the analysis. The variance inflation factor will be computed as the ratio of the actual to effective sample size, and the required sample size will be updated by multiplying the required sample size (approximately 364 patients per cohort) by the variance inflation factor.

9.11.2.5. Stratified Analyses

Where sample size permits, stratified/subgroup analyses of all outcomes will be conducted that consider the timing of exposure (earliest trimester of exposure), extent of exposure (cumulative dose during pregnancy or relevant exposure window), country, BMI category at conception, maternal age group at conception (<18 years, 18 to 34 years, 35 to 44 years, and 45 to 50 years), and maternal race and ethnicity.

9.11.2.6. Supplementary Analyses

Supplementary descriptive analyses of all outcomes will be conducted as specified for the main analysis population but that include pregnant individuals who were excluded from the main analysis population due to:

- Occurrence of the pregnancy outcome prior to enrollment (retrospectively enrolled participants)
- Exposure to a known teratogen or an investigational medication during or prior to pregnancy (teratogen/investigational medication-exposed participants)
- Exposure to other GLP-1 RA therapies during pregnancy or within 5 times the half-life of the drug prior to conception among the tirzepatide exposed cohort
- Treatment with tirzepatide during pregnancy for reasons other than weight management among the tirzepatide-exposed cohort
- Inclusion of a prior pregnancy in the analysis population (subsequent pregnancies)

9.11.2.7. Sensitivity Analyses

Sensitivity analyses will also be conducted to examine the extent to which changes in certain methods or assumptions affect the results. The following sensitivity analyses are planned:

- As described in Section 9.11.1.1.3, a sensitivity analysis will be conducted that applies a stricter definition of prospective enrollment. For this analysis, individuals who enroll or make initial contact with the registry prior to diagnostic prenatal testing (and prior to pregnancy outcome) will be considered prospectively enrolled, and individuals who enroll or make initial contact with the registry after diagnostic prenatal testing, regardless of the results, will be considered retrospectively enrolled in addition to individuals who enroll after pregnancy outcome. The outcomes of individuals who enroll prior to diagnostic prenatal testing will be compared with those of individuals who enrolled after diagnostic prenatal testing.
- As described in Sections 9.11.1.1.6 and 9.11.1.1.7, additional pregnancies within the same participant are excluded from the analysis population and multiple gestations are excluded from certain calculations. The assumption is that both scenarios will be relatively rare. However, if 10% or more of the participants have more than 1 pregnancy in the registry or if 10% or more have multiple gestation pregnancies, a corresponding sensitivity analyses of all outcomes of interest will be conducted that account for the correlation between previous and subsequent pregnancies in the same participant and multiple gestation pregnancies using mixed models. If percentage is less than 10%, attempting to model the correlation will likely result in a failure of model convergence.[106]

- To test the robustness of the IPTW method (Section 9.11.2.4), a sensitivity analysis will be conducted by stratifying the PS into five quantiles as an alternative to IPTW and comparing the results. Within each stratum, the effect of treatment on outcomes can be estimated by comparing outcomes directly between tirzepatide and comparator participants. The stratum-specific estimates of treatment effect can then be pooled across stratum to estimate an overall treatment effect.[107] In addition to a truncation method, trimming will be used to assess any influence of excluding extreme weights in a sensitivity analysis.
- Sensitivity analyses will also be conducted to assess the potential impact of missing data and/or unmeasured confounding (e.g., quantitative bias analysis to estimate the overall strength of potential unmeasured confounding required to nullify the estimated treatment effect or reverse the statistical inference).[108]
- A sensitivity analysis will be conducted that limits the tirzepatide exposed and the AOM active comparator cohorts to individuals with a diagnosis of obesity, or overweight with at least one weight-related comorbid condition at the time of conception.
- A sensitivity analysis will be conducted that expands the tirzepatide exposed cohort to individuals exposed to any other weight loss medications (including GLP-1 RAs) other than tirzepatide.
- In the main analysis, maternal use of within 5 half-lives of the respective medication is defined as a potential fetal exposure to medication use during pregnancy. This is a conservative estimate which may dilute a potential association between medication and the study outcomes. Sensitivity analysis will be conducted with shorter half-lives (i.e., 1-, 2- and 3-times half-lives) to define fetal exposure to medication use during pregnancy.
- Pregnant individuals who are exposed to a known teratogen or an investigational medication during or prior to pregnancy will be excluded from the main analysis population and described in the supplementary analyses. In the case that there are more than 10% of pregnant individuals with teratogen exposure during or prior to pregnancy, an additional sensitivity analysis will be considered by retaining those individuals in the analysis and addressing potential impact of teratogen exposure via analytical adjustment. More details will be included in the SAP.

9.11.2.8. Missing Data

For critical data points, missing values are expected to be minimal, thereby negating the need for imputation. As is described in Section 9.6.1, the registry will make multiple attempts to obtain missing data for critical data points. The frequency and percentage of participants with missing data for each data point will be presented.

For start and end dates of medical conditions or exposures, if the month and year are known but the day is missing, then the day will be imputed for analyses: missing start dates will be set to the first day of the month, and missing end dates will be set to the last day of the month. Listings will continue to present the day as missing.

If there is a high degree of missing covariate data (≥10%), multiple imputation may be considered to minimize the loss of observations in the analysis by creating the set of weights for each imputed dataset and then averaging them into a single treatment effect estimate.[104,105]

9.11.2.9. Interim Analysis

The registry will produce annual internal summary reports for review by the Scientific Advisory Committee (SAC) each year beginning in June 2026 (see Section 9.20 for a description of SAC responsibilities). Study reports will be submitted to the FDA every two years beginning in 2026. Reports will comprise recruitment and retention including non-promotional strategies raising awareness of the registry, enrollment, and results to date.

Until enough data have accumulated to warrant a full comparative analysis, reports will be abbreviated and include only results of descriptive analyses, such as enrollment and outcomes of pregnancy and pediatric follow-up.

Empirical evaluation of the PS distributions is planned when 100 participants have been enrolled in each of the 3 cohorts. At this point, a decision will be made as to whether there is sufficient overlap between the cohorts (the 2 comparisons treated separately) to achieve the desired power in the analysis or whether larger numbers of participants may need to be enrolled (see Section 9.11.2.4). The outcome will not be inspected between treatment cohorts during this assessment.

9.12. Quality Control

Data quality control will be performed on active sites (research coordination centers in each country that have enrolled at least 1 patient). Quality control will be performed by qualified, designated personnel in each county.

Ensuring that the data obtained and delivered to the sponsor are of high quality will be an ongoing, multistep process involving programming of edit checks for critical data variables in the electronic data capture system and visual review for completeness, logic, consistency, and accuracy. As is recommended in regulatory guidance documents, data collection forms have been carefully designed to ensure data quality and integrity. Participant-reported data may be verified by the appropriate HCP. PPD will follow their standard operating procedures (SOPs) as they relate to training of personnel, data handling, and processing, complying with 21 Code of Federal Regulations (CFR) Part II and Good Pharmacoepidemiology Practice (GPP).

9.12.1. Monitoring Procedures

During the course of the study, monitoring should be performed to ensure that the protocol has been adhered to.

9.12.2. Critical Documents

Before the study is started (which is when informed consent is obtained from the first participant), the following documents must be available to Eli Lilly and PPD:

- Regulatory approval and/or notification as required
- Documentation of the principal investigator/co-investigator's qualifications (for instance a short curriculum vitae or authorization)
- Signed and dated agreement on the final protocol

- Approval/favorable opinion from IRB/IEC (or other appropriate bodies as required locally) clearly identifying the documents reviewed: the protocol including version, participant information/informed consent form and any other written information to be provided to the participant, participant enrollment procedures
- Copy of IRB/IEC approved participant information/informed consent form/any other written information/advertisement (or waiver by IRB/IEC of documentation of informed consent)

9.12.3. Retention of Study Documentation

Eli Lilly and PPD will comply with GPP and relevant national legislation related to archiving of study documentation.

The central registry site must agree to archive the documentation pertaining to the study in an archive for at least 5 years after final report/first publication of the study, whichever comes later. The central registry site should not destroy any documents without prior permission from Eli Lilly.

Eli Lilly will retain the documentation pertaining to the study according to company procedure and in accordance with national regulations if they require a longer retention period.

9.13. Limitations of the Research Methods

Because this is an NIS, potential confounding factors cannot be ruled out. Data collection will reflect routine clinical practice rather than mandatory assessments at pre-specified time points, which may have an impact on the amount of data and its interpretation.

The general limitations of pregnancy registries with voluntary participation are well known, and these will apply to this study as well. One key limitation of the study is the limited size of the population of pregnant individuals expected to be exposed to tirzepatide for weight management during pregnancy.

Another key limitation of the registry, due to the voluntary nature of participation, relates to representativeness. Since participation in the registry is voluntary, the pregnant individuals who voluntarily enroll in the registry may not be representative of the overall population of pregnant individuals. This could introduce selection bias and affect the generalizability of the results. To minimize the potential for selection bias, a multi-faceted awareness strategy will be employed.

Because the registry will enroll individuals only after recognition of pregnancy and in some cases much later during pregnancy, there will be left truncation of the enrolled population. That is, the enrolled population of pregnant individuals will include individuals with a shortened period at risk of the outcomes and exclude individuals who have already had certain outcomes (e.g., SAB, induced abortion).

Additionally, individuals in the tirzepatide cohort may differ from those in the unexposed cohorts in important factors that could impact pregnancy outcomes (e.g., access to healthcare and medications, socioeconomic status, disease severity, etc.). To partly address this concern, this study includes two comparator cohorts, an AOM active comparator cohort, and an AOM

unexposed comparator cohort that has obesity or overweight with comorbidities at the time of conception.

> As described in Section 9.11.2, prevalence of the outcomes among the tirzepatide exposed cohort will be compared with each of the two comparator cohorts. The adjusted comparison of the prevalence of MCM observed in the tirzepatide exposed relative to the unexposed comparator cohorts will be considered the primary analysis. Because participants who seek and receive pharmacotherapy for weight management may have greater disease severity, confounding by indication (also known as channeling bias) will need to be carefully considered for the comparison. Confounding by indication can occur when participant characteristics, such as disease severity, affect prescribing patterns. If not accounted for in the analysis, such confounding could result in an apparent increased risk of the outcomes associated with medication use. To minimize the impact of potential confounders, the registry will record the characteristics of individuals in both exposed and unexposed comparator cohorts and use statistical methods to examine and account for any differences between cohorts in the analysis. The registry will employ identical data collection and follow-up procedures across the registry cohorts to minimize any potential bias. As is described in Section 9.11.2, this study will employ the IPW method to address the imbalance between cohorts. Although statistical methods will be used to account for confounding or mediating variables, it may not be possible to control for all variables (e.g., unknown) that could influence the results of the study. Therefore, some important confounders (either measured or not) could still be unbalanced.

Since the registry is focused on prospective enrollment, misclassification of drug exposure is non-differential regarding outcome. However, outcome misclassification could occur, especially regarding minor congenital malformations that may be overlooked or unreported. Although some MCMs may not be easily visible at birth, most will be apparent by 12 months of age, so misclassification of these outcomes is expected to be minimal in this registry, which aims to follow infants through 12 months of age.

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

Pregnancies that result in fetal losses (stillbirths, SABs, and induced abortions) without reported MCMs may introduce a classification bias. The percentage of these pregnancies consisting of potentially normal outcomes or MCMs is unknown. The data collection form attempts to obtain information on MCMs detected at the time of the outcome. However, the reporting HCP may not know the condition of the lost fetus. Additionally, recent changes in legislation around abortion within the US may lead to underreporting and/or misclassification of outcomes due to both patient and HCP concerns around legal repercussions of reporting.

Each source of potential bias will be evaluated descriptively and discussed in the report.

9.14. Other Aspects

Taking advantage of the prospective nature of registry studies, the Tirzepatide Pregnancy Registry study aims to collect comprehensive data on adverse pregnancy outcomes in patients treated with tirzepatide during pregnancy. The extended efforts include: (1) evaluation of additional exploratory outcomes such as hyperemesis gravidarum, maternal cardiac disease, large for gestational age, and inadequate/rapid gestational weight gain that have been associated with maternal obesity; and (2) inclusive enrollment of individuals prescribed tirzepatide for indications other than weight management for a descriptive analysis (see Sections 9.11.1.1.2 and 9.11.2.6).

9.15. Protection of Human Subjects

Observational studies will be submitted to ethical review boards (ERBs) for approval whenever required by local law. Regulatory authorities will be notified and approval sought as required by local laws and regulations. Progress reports will be submitted to ERBs and regulatory authorities as required by local laws and regulations.

This study will be conducted in accordance with applicable laws and regulations of the region, country, or countries where the study is being conducted, as appropriate.

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

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

Exemption of Health Insurance Portability and Accountability Act Authorization (Applicable for US participants only)

As a post-marketing safety reporting activity, this registry meets the following criteria and is therefore exempt from the US Health Insurance Portability and Accountability Act (HIPAA) authorization.

The CFR, in 45 CFR 164.512, states:

(iii) A person subject to the jurisdiction of the Food and Drug Administration (FDA) with respect to an FDA-regulated product or activity for which that person has responsibility, for the purpose of activities related to the quality, safety or effectiveness of such FDA-regulated product or activity. Such purposes include:

- To collect or report AEs (or similar activities with respect to food or dietary supplements), product defects or problems (including problems with the use or labelling of a product), or biological product deviations;
- To track FDA-regulated products;
- To enable product recalls, repairs, or replacement, or lookback (including locating and notifying individuals who have received products that have been recalled, withdrawn, or are the subject of lookback); or
- To conduct post marketing surveillance

To further clarify this issue, an article published by the Pregnancy Labeling Task Force, US FDA, states:

> The HIPAA Privacy Rule specifically permits the disclosure of protected health information by covered entities such as HCPs or hospitals for public health purposes related to the quality, effectiveness, and safety of FDA-regulated products to both the manufacturers and directly to the FDA. This includes collecting or reporting AEs, tracking FDA-regulated products and conducting post-marketing surveillance to comply with requirements or at the direction of the FDA.[109]

Regulatory and Ethical Compliance

This study was designed and shall be implemented and reported in accordance with GPP,[110] with applicable local regulations and with the ethical principles established in the Declaration of Helsinki. The protocol will be submitted to the applicable regulatory authorities and IRBs/IECs for approval prior to registry implementation. The protocol, informed consent forms, and waiver of documentation of informed consent will be reviewed and approved by IRBs/IECs before study implementation. A signed and dated statement that the protocol and waiver have been approved by the IRBs/IECs will be given to the sponsor before study initiation. Prior to study start, the investigator will sign a protocol signature page confirming their agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol. If an inspection of the site is requested by a regulatory authority, the investigator must inform the sponsor immediately that this request has been made.

9.16. Informed Consent Form for Study Participants

Informed consent will be obtained for each registry participant. Where allowed by local laws and regulations (currently only in US), adult participants will be given the option to provide verbal consent under the waiver of documentation of informed consent or signed informed consent through the web-based/mobile application or via courier. For the registry, adults are defined as individuals who have attained the legal age for consenting to treatments, procedures, or clinical investigations under applicable law in various countries and US states.

Minors are defined as individuals who have not attained the legal age for consenting to treatments, procedures, or clinical investigations under applicable law in various countries and US states. The definitions of a minor and an emancipated minor vary by country (and state, within the US). This registry will follow applicable laws for the country/state in which the participant resides. If a minor requests participation in the registry and all eligibility criteria are met, the registry will obtain assent from the minor and signed written consent from a parent or guardian through the web-based/mobile application or via courier. Written consent from both parent(s) or both guardian(s) will be obtained in the countries/states in which this is required by local laws and regulations.

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

Additional Safeguards for Children in Clinical Investigations

Although this registry involves the collection of information on infants after birth, the registry protocol will be conducted in full consideration of 21 CFR Part 50, Subpart D, Additional Safeguards for Children in Clinical Investigations (for FDA-regulated human subjects research) and applicable regulations in other countries. This registry will ascertain maternal and infant information only via maternal and pediatric HCPs, and no clinical specimens will be collected from the infants; therefore, data collected on infants of individuals in this pregnancy registry involves no greater than minimal risk to the infants. Although the infants will be too young to provide assent, the registry protocol will require permission from the mothers, and they will be asked to provide authorization for release of medical information from their infants' HCPs.

Electronic Informed Consent Process

The website will contain information about the registry and will provide access to the study web-based/mobile application. Via the web-based/mobile application, the individual will register with their computer or mobile device using credentials (i.e., name, email address, and password).

Once the individual has registered, the application will automatically start the consent process. The application will present the contents of the consent in a scrollable window. The individual will review the document, and the application will present the following options: 'Hold', 'Disagree', and 'Sign and Publish'.

If the individual has questions during the consent process, they will be encouraged to stop the consenting process on the application via the 'Hold' button and call the VRCC, where study specialists will assist with any questions. The individual can resume completion of the consent process at any time. If the individual does not wish to provide consent, they will be directed to choose the 'Disagree' option, and the process will stop. If the individual wishes to provide consent, they will be directed to choose 'Sign and Publish'.

The application will provide an option for the individual to view or email their completed consent form(s).

After the informed consent, the individual will complete the medical release form(s) and answer some basic medical information questions.

Waiver of Documentation of Informed Consent

The following US regulations indicate that waiver of documentation of informed consent is appropriate for this registry.

As is stated in US CFR, 21 CFR 56.109 (and additionally in 45 CFR 46.117(c)(2)):

(c) An IRB shall require documentation of informed consent in accordance with 50.27 of this chapter, except as follows:

(1) The IRB may, for some or all subjects, waive the requirement that the subject, or the subject's legally authorized representative, sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context

(d) In cases where the documentation requirement is waived under paragraph (c)(1) of this section, the IRB may require the investigator to provide subjects with a written statement regarding the research.

The research involves no more than minimal risk to the participants. This is an observational study that involves no experimental intervention and poses no possibility of physical harm. The only potential risk is a breach of confidentiality, and the registry has well-established procedures in place to prevent any such breach of confidentiality. Extensive safeguards are in place to ensure that participants' privacy is protected:

a. An adequate plan is provided to protect the identifiers from improper use and disclosure.
   - An adequate plan is provided to remove the identifiers at the earliest opportunity.
   - Adequate assurances are provided that the protected health information will not be reused or disclosed to any other person or entity.

The research involves no procedures for which written consent is normally required outside the research context. Enrollment in this observational study will be strictly voluntary, and participants can withdraw their consent to participate at any time. The schedule of participant visits and all treatment regimens will be at the discretion of the treating HCP. Data submitted to the registry will be limited to data routinely collected and documented in the participant's medical record.

9.17. Data Handling

If the participant (or the participant's LAR) withdraws the previously given informed consent, the participant's data will be handled as follows:

- Data collected will be used as part of the statistical analysis

- Safety events will be reported to Global Safety, Eli Lilly/health authorities

Data will be collected and handled in accordance with local law and IRB/IEC procedures.

9.18. IRB/IEC, Health Authorities, and Premature Termination of the Study

Study-specific documentation (for example, study protocol, Participant Information/Informed Consent Form, participant materials) must be submitted to the relevant national bodies as required by national regulation and procedures in the participating countries.

The study must be approved by the IRB/IEC for each participating country.

In accordance with regulatory requirements, including Good Pharmacovigilance Practices (GVP), the sponsor will inform the health authorities of AEs reported in patients treated with tirzepatide.

9.19. Premature Termination of the Study

The sponsor may decide, in agreement with regulatory authorities, to stop the study or part of the study at any time.

Prior to making a final decision regarding the premature termination of the study, information will be provided to the relevant regulatory authorities.

9.20. Responsibilities

Sponsor

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

Principal Investigator/Co-Investigator

The principal investigator/co-investigator is responsible for providing oversight of the registry and all submissions (protocol, amendments) to the IRBs/IECs. The principal investigator/co-investigator may delegate responsibilities for study-related tasks where appropriate to individuals who are sufficiently qualified by education, training, and experience, in accordance with applicable regulations. The principal investigator will be available to the sponsor and the SAC for ongoing consultations regarding the review, analysis, and conduct of the registry.

Virtual Registry Coordination Center (VRCC)

The VRCC is responsible for assisting the principal investigator/co-investigator in all aspects of participant recruitment, informed consent, data collection, and management. As is noted in Section 9.15, the VRCC staff is fully trained on and compliant with SOPs regarding the protection of human subjects and data privacy.

Scientific Advisory Committee

The SAC is responsible for overseeing the scientific affairs of the registry, including its ongoing monitoring. The SAC is an independent (not associated with the Sponsor) group of recognized experts in the fields of teratology, epidemiology, maternal and fetal medicine, and therapeutic areas from academia and private practice. They will meet prior to finalization of each summary report, to review and classify reported MCMs (as described in Section 9.7.3) and to review the accumulated body of data from the registry and to carry out any actions required, including review of recruitment and retention, and review and interpretation of analyses, reports, and publications of registry data. As warranted, the SAC may recommend specific strategies to heighten awareness of the registry. The SAC may meet on ad hoc occasions, if indicated, to address potential signals or other issues that arise during the registry.

The responsibilities of the SAC will be described in a charter to which each SAC member will agree.

10. Management and Reporting of Adverse Events/Adverse Reactions

10.1. Primary Data Collection Study

The study personnel will collect via electronic data entry/written data collection form all protocol-defined adverse events (AEs), including all associated fatal outcomes, occurring in temporal association with Lilly product(s) and comparator product(s) (as applicable) that are under evaluation as defined in this protocol. The protocol-defined AEs include specific maternal, fetal, and infant outcomes (Section 9.7.3).

The items in the list below are not protocol-defined AEs; however, the nature of the registry is such that these events may be encountered and will therefore follow the collection process above.

- Pregnancy exposure
- Breastfeeding exposure

Adverse events collected will be summarized in the interim safety reports and in the final study report.

All other AEs will not be actively collected due to lack of relevance to the study objectives. However, non-protocol defined AEs and other safety information may be reported in the course of participant interviews. Study personnel are requested to report any Suspected Adverse Reactions (SARs) with Lilly products not under evaluation in this protocol or SARs with non-Lilly products to the appropriate party (for example, regulators or the marketing authorization holder) as they would in normal practice.

Study personnel are not obligated to actively collect AEs or serious AEs (SAEs) in patients once they have discontinued from the study. However, if the study personnel learn of any SAE, including death, at any time after the patient has discontinued from the study and the event is considered reasonably possibly related to the Lilly product under evaluation, the study personnel must promptly notify Lilly.

10.1.1. Serious Adverse Events

The study personnel will report to Lilly or its designee any protocol-defined SAE arising in temporal association with the Lilly product(s) under evaluation within 24 hours of awareness of the event via a sponsor-approved method. Reports issued via telephone are to be immediately followed with official notification on study-specific SAE forms. A protocol-defined SAE is any AE from this study that results in one of the following outcomes:

- Death
- Initial or prolonged inpatient hospitalization
- A life-threatening experience (that is, immediate risk of dying)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect

- Or is an important medical event 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 above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

When a condition related to the tirzepatide delivery system necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure, the serious outcome of "required intervention" will be assigned.

10.1.2. Nonserious Adverse Events

The study personnel will record any **nonserious,** protocol-defined AEs arising in temporal association with the Lilly product(s) under evaluation within 30 days of awareness of the event via electronic data entry/written data collection form. Lilly or its designee will execute the extraction for EU sites to comply with the regulatory reporting requirements.

10.2. Product Complaints

Lilly collects product complaints on marketed Lilly products such as drugs, drug/device combinations, medical devices, software as medical device (e.g., mobile medical applications), and comparator product(s) used in post-marketing medical research studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

For Lilly products under evaluation and/or Lilly products not under evaluation but discovered in the course of the study, study personnel are instructed to report product complaints as they would for products in the marketplace.

For non-Lilly products, such as comparator drugs or medical devices, or concomitant drugs or medical devices, study personnel are instructed to report product complaints as they would for products in the marketplace.

11. Plans for Disseminating and Communicating Study Results

The registry will produce interim and final study reports that will be submitted to regulatory authorities. Abbreviated interim reports will be produced until enough participants have been enrolled for comparative analyses and will be limited to descriptive analyses such as disposition and outcomes summaries.

Final reports will be submitted to regulatory agencies. The study, including the final report, will also be registered in the Heads of Medicines Agencies European Medicines Agency Catalogue of Real-World Data Sources and Studies.

The study findings may be submitted to a scientific congress and/or to a peer-reviewed journal.

12. References

1. Eli Lilly. Zepbound® (tirzepatide), US prescribing Information (PI). 2024. Accessed April 2024 https://pi.lilly.com/us/zepbound-uspi.pdf
2. ClinicalTrials.gov. A Study of Tirzepatide (LY3298176) in Healthy Lactating Females. 2024. Accessed April 2024 https://clinicaltrials.gov/study/NCT05978713?cond=Tirzepatide&rank=2
3. Aronne LJ, Sattar N, Horn D, et al. Continued Treatment With Tirzepatide for Maintenance of Weight Reduction in Adults With Obesity. The SURMOUNT-4 Randomized Clinical Trial. *JAMA*. 2024;331(1):38-48.
4. Wadden TA, Chao AM, Machineni S, et al. Tirzepatide after intensive lifestyle intervention in adults with overweight or obesity: the SURMOUNT-3 phase 3 trial. *Natural Medicine*. 2023;29:2909-2918.
5. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide Once Weekly for the Treatment of Obesity. *N Engl J Med*. 2022;387(3):205-216. doi:10.1056/NEJMoa2206038
6. Garvey WT, Frias JP, Jastreboff AM, et al. Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet*. 2023;402(10402):613-626. doi:10.1016/S0140-6736(23)01200-X
7. Cesta CE, Rotem R, Bateman BT, et al. Safety of GLP-1 Receptor agonists and other second-line antidiabetics in early pregnancy. *JAMA Internal Medicine*. 2024;184(2):144-152.
8. Dao K, Shechtman S, Weber-Schoendorfer C, et al. Use of GLP1 receptor agonists in early pregnancy and reproductive safety: a multicentre, observational, prospective cohort study based on the databases of six Teratology Information Services. *BMJ Open*. 2024;14(4):e083550. doi:10.1136/bmjopen-2023-083550
9. World Health Organization (WHO). WHO Fact sheet: Obesity and overweight. 2021. Accessed January 25, 2022. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
10. Kelly T, Yang W, Chen CS, Reynolds K, He J. Global burden of obesity in 2005 and projections to 2030. *Int J Obes (Lond)*. 2008;32(9):1431-1437. doi:10.1038/ijo.2008.102
11. NCD Risk Factor Collaboration. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. *Lancet*. 2016;387(10026):1377-1396. doi:10.1016/S0140-6736(16)30054-X
12. Dutton GR, Kim Y, Jacobs DR, et al. 25-year weight gain in a racially balanced sample of U.S. adults: The CARDIA study. *Obesity (Silver Spring)*. 2016;24(9):1962-1968. doi:10.1002/oby.21573
13. Gordon-Larsen P, The NS, Adair LS. Longitudinal trends in obesity in the United States from adolescence to the third decade of life. *Obesity (Silver Spring)*. 2010;18(9):1801-1804. doi:10.1038/oby.2009.451
14. Norman JE, Bild D, Lewis CE, Liu K, West DS, Study C. The impact of weight change on cardiovascular disease risk factors in young black and white adults: the CARDIA study. *Int J Obes Relat Metab Disord*. 2003;27(3):369-376. doi:10.1038/sj.ijo.0802243

15. Zheng Y, Manson JE, Yuan C, et al. Associations of Weight Gain From Early to Middle Adulthood With Major Health Outcomes Later in Life. *JAMA*. 2017;318(3):255-269. doi:10.1001/jama.2017.7092
16. Wang MC, Freaney PM, Perak AM, et al. Trends in Prepregnancy Obesity and Association With Adverse Pregnancy Outcomes in the United States, 2013 to 2018. *J Am Heart Assoc*. 2021;10(17):e020717. doi:10.1161/JAHA.120.020717
17. Athukorala C, Rumbold AR, Willson KJ, Crowther CA. The risk of adverse pregnancy outcomes in women who are overweight or obese. *BMC Pregnancy Childbirth*. 2010;10:56. doi:10.1186/1471-2393-10-56
18. Chen C, Xu X, Yan Y. Estimated global overweight and obesity burden in pregnant women based on panel data model. *PLoS One*. 2018;13(8):e0202183. doi:10.1371/journal.pone.0202183
19. Oteng-Ntim E, Kopeika J, Seed P, Wandiembe S, Doyle P. Impact of obesity on pregnancy outcome in different ethnic groups: calculating population attributable fractions. *PLoS One*. 2013;8(1):e53749. doi:10.1371/journal.pone.0053749
20. Lashen H, Fear K, Sturdee DW. Obesity is associated with increased risk of first trimester and recurrent miscarriage: matched case-control study. *Hum Reprod*. 2004;19(7):1644-1646. doi:10.1093/humrep/deh277
21. Yao R, Ananth CV, Park BY, Pereira L, Plante LA, Consortium PR. Obesity and the risk of stillbirth: a population-based cohort study. *Am J Obstet Gynecol*. 2014;210(5):457.e451-459. doi:10.1016/j.ajog.2014.01.044
22. Lynch AM, Hart JE, Agwu OC, Fisher BM, West NA, Gibbs RS. Association of extremes of prepregnancy BMI with the clinical presentations of preterm birth. *Am J Obstet Gynecol*. 2014;210(5):428.e421-429. doi:10.1016/j.ajog.2013.12.011
23. Salihu HM, Luke S, Alio AP, Deutsch A, Marty PJ. The impact of obesity on spontaneous and medically indicated preterm birth among adolescent mothers. *Arch Gynecol Obstet*. 2010;282(2):127-134. doi:10.1007/s00404-009-1213-y
24. Sewell, MF H-PL, Super DM, Catalano P. Increasedneonatal fat mass, not lean body mass, is associated with maternal obesity. AmJ Obstet Gynecol 2006;195(4):1100-3.
25. Stothard KJ, Tennant PW, Bell R, Rankin J. Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. *JAMA*. 2009;301(6):636-650. doi:10.1001/jama.2009.113
26. Persson M, Cnattingius S, Villamor E, et al. Risk of major congenital malformations in relation to maternal overweight and obesity severity: cohort study of 1.2 million singletons. *BMJ*. 2017;357:j2563. doi:10.1136/bmj.j2563
27. Bodnar LM, Ness RB, Markovic N, Roberts JM. The risk of preeclampsia rises with increasing prepregnancy body mass index. *Ann Epidemiol*. 2005;15(7):475-482.
28. Chu SY, Callaghan WM, Kim SY, et al. Maternal obesity and risk of gestational diabetes mellitus. *Diabetes Care*. 2007;30(8):2070-2076. doi:10.2337/dc06-2559a
29. Gaillard R, Steegers E, Hofman A, Jaddoe V. Associations of maternal obesity with blood pressure and the risks of gestational hypertensive disorders. The Generation R Study. *J Hypertension*. 2011;29(5):937-944. doi:10.1097/HJH.0b013e328345500c
30. Vikanes A, Grjibovski AM, Vangen S, Gunnes N, Samuelsen SO, Magnus P. Maternal body composition, smoking, and hyperemesis gravidarum. *Ann Epidemiol*. 2010;20(8):592-598. doi:10.1016/j.annepidem.2010.05.009. PMID: 20609338

31. Gilley SP, Harrall KK, Friedman C, et al. Association of Maternal BMI and Rapid Infant Weight Gain with Childhood Body Size and Composition. Pediatrics. 2023 May 1;151(5):e2022059244. *Pediatrics*. 2023;151(5):e2022059244.
32. Arisaka O, Ichikawa G, Koyama S, Sairenchi T. Childhood obesity: rapid weight gain in early childhood and subsequent cardiometabolic risk. *Clinical Pediatric Endocrinology*. 2020;29(4):135-142.
33. Brion MJ, Zeegers M, Jaddoe V, et al. Intrauterine effects of maternal prepregnancy overweight on child cognition and behavior in 2 cohorts. *Pediatrics*. 2011;127(1):e202-e211. doi:10.1542/peds.2010-0651
34. Apovian CM, Aronne LJ, Bessesen DH, et al. Pharmacological management of obesity: an endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2015;100(2):342-362. doi:10.1210/jc.2014-3415
35. Dombrowski SU, Knittle K, Avenell A, Araujo-Soares V, Sniehotta FF. Long term maintenance of weight loss with non-surgical interventions in obese adults: systematic review and meta-analyses of randomised controlled trials. *BMJ*. 2014;348:g2646. doi:10.1136/bmj.g2646
36. Ferguson C, David S, Divine L, Kahan S, Gallagher C, Gooding M. Obesity Drug Outcome Measures. A Consensus Report of Considerations Regarding Pharmacologic Intervention. 2012. Accessed August 2018, https://stop.publichealth.gwu.edu/sites/g/files/zaxdzs4356/files/2022-02/obesitydrugmeasures.pdf
37. Pasman WJ, Saris WH, Westerterp-Plantenga MS. Predictors of weight maintenance. *Obes Res*. 1999;7(1):43-50. doi:10.1002/j.1550-8528.1999.tb00389.x
38. Sumithran P, Prendergast LA, Delbridge E, et al. Long-term persistence of hormonal adaptations to weight loss. *N Engl J Med*. 2011;365(17):1597-1604. doi:10.1056/NEJMoa1105816
39. Toplak H, Woodward E, Yumuk V, Oppert JM, Halford JC, Fruhbeck G. 2014 EASO Position Statement on the Use of Anti-Obesity Drugs. *Obes Facts*. 2015;8(3):166-174. doi:10.1159/000430801
40. Wilding JP, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med*. 2021;384(11):989-1002.
41. Moses RG, Casey SA, Quinn EG, et al. Pregnancy and Glycemic Index Outcomes study: effects of low glycemic index compared with conventional dietary advice on selected pregnancy outcomes. *Am J Clin Nutr*. 2014;99(3):517-523. doi:10.3945/ajcn.113.074138
42. Santos IA, Stein R, Fuchs SC, et al. Aerobic exercise and submaximal functional capacity in overweight pregnant women: a randomized trial. *Obstet Gynecol*. 2005;106(2):243-249. doi:10.1097/01.AOG.0000171113.36624.86
43. Peccei A, Blake-Lamb T, Rahilly D, Hatoum I, Bryant A. Intensive Prenatal Nutrition Counseling in a Community Health Setting: A Randomized Controlled Trial. *Obstet Gynecol*. 2017;130(2):423-432. doi:10.1097/AOG.0000000000002134
44. Furber CM, McGowan L, Bower P, Kontopantelis E, Quenby S, Lavender T. *Antenatal interventions for reducing weight in obese women for improving pregnancy outcome (review)*. John Wiley & Sons; 2013.
45. Food and Drug Administration (FDA). Postapproval pregnancy safety studies: guidance for industry. 2019. Accessed January 25, 2022. https://www.fda.gov/media/124746/download

46. Muller DRP, Stenvers DJ, Malekzadeh A, Holleman F, Painter RC, Siegelaar SE. Effects of GLP-1 agonists and SGLT2 inhibitors during pregnancy and lactation on offspring outcomes: a systematic review of the evidence. *Front Endocrinol (Lausanne)*. 2023;14:1215356. doi:10.3389/fendo.2023.1215356
47. [FDA] Food and Drug Administration. Collection of race and ethnicity data in clinical trials and clinical studies for FDA-regulated medical products. Guidance for industry. Published January 2024. Accessed February 11, 2025. https://www.fda.gov/media/175746/download
48. Centers for Disease Control and Prevention (CDC). Birth defects surveillance toolkit 1.4 Congenital anomalies – definitions. 2020. Accessed January 25, 2022. https://stacks.cdc.gov/view/cdc/100349
49. Centers for Disease Control and Prevention (CDC). Division of Birth Defects and Developmental Disabilities. Birth defects and genetic diseases branch 6-digit codes for reportable congenital anomalies. 2021a. Accessed January 25, 2022. https://www.cdc.gov/birth-defects/tracking/index.html
50. European Surveillance of Congenital Anomalies (EUROCAT). EUROCAT Guide1.4 and Reference Documents. 2021. Accessed January 25, 2022. https://eu-rd-platform.jrc.ec.europa.eu/system/files/public/JRC-EUROCAT-Full-Guide-1.4-version-07-Oct-2021.pdf
51. Holmes LB, Westgate MN. Inclusion and exclusion criteria for malformations in newborn infants exposed to potential teratogens. *Birth Defects Res A Clin Mol Teratol*. 2011;91(9):807-812. doi:10.1002/bdra.20842
52. Centers for Disease Control and Prevention (CDC). Division of Birth Defects and Developmental Disabilities. Birth defects toolkit. Appendix B: external minor congenital anomalies. 2019. Accessed January 25, 2022. https://stacks.cdc.gov/view/cdc/100349
53. American College of Obstetricians and Gynecologists. Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin Summary, Number 222. *Obstet Gynecol*. 2020;135(6):1492-1495.
54. Giwa A, Nguyen M. Late onset postpartum preeclampsia 3 months after delivery. *Am J Emerg Med*. 2017;35(10):1582 e1581-1582 e1583. doi:10.1016/j.ajem.2017.07.024
55. American Diabetes Association. Gestational diabetes mellitus. *Diabetes Care*. 2004;27(1):S88-S90.
56. American College of Obstetricians and Gynecologists. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. *Obstet Gynecol*. 2002;99(1):159-167.
57. Levine MG, Esser D. Total parenteral nutrition for the treatment of severe hyperemesis gravidarum: maternal nutritional effects and fetal outcome. *Obstet Gynecol*. 1988;72(1):102-107.
58. Institute of Medicine (US), National Research Council (US) Committee to Reexamine IOM Pregnancy Weight Guidelines. *Weight Gain During Pregnancy: Reexamining the Guidelines. PMID: 20669500*. National Academies Press (US); 2009.
59. American College of Obstetricians and Gynecologists (ACOG). ACOG Obstetric Care Consensus No.10: management of stillbirth. *Obstet Gynecol*. 2020;135(3):e110-132.
60. Centers for Disease Control and Prevention (CDC). CDC's Abortion Surveillance System FAQs. 2024. Accessed June 2024, https://www.cdc.gov/reproductive-health/data-statistics/abortion-surveillance-system.html

61. Battaglia FC, Lubchenco LO. A practical classification of newborn infants by weight and gestational age. *J Pediatr*. 1967;71(2):159-163. doi:10.1016/s0022-3476(67)80066-0
62. Villar J, Cheikh Ismail L, Victora CG, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. *Lancet*. 2014;384(9946):857-868. doi:10.1016/S0140-6736(14)60932-6
63. Villar J, Giuliani F, Fenton TR, et al. INTERGROWTH-21st very preterm size at birth reference charts. *Lancet*. 2016;387(10021):844-845. doi:10.1016/S0140-6736(16)00384-6
64. Chiavaroli V, Derraik JG, Hofman PL, Cutfield WS. Born Large for Gestational Age: Bigger Is Not Always Better. *J Pediatr*. 2016;170:307-311. doi:10.1016/j.jpeds.2015.11.043
65. Flores-Barrantes P, Iguacel I, Iglesia-Altaba I, Moreno LA, Rodríguez G. Rapid weight gain, infant feeding practices, and subsequent body mass index trajectories: the CALINA study. *Nutrients*. 2020;12(10):3178. doi:10.3390/nu12103178
66. Monteiro PO, Victora CG. Rapid growth in infancy and childhood and obesity in later life--a systematic review. *Obes Rev*. 2005;6(2):143-154. doi:10.1111/j.1467-789X.2005.00183.x.
67. World Health Organization (WHO). WHO child growth standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development. 2006. Accessed June 2024. https://www.who.int/publications/i/item/924154693X
68. Centers for Disease Control and Prevention (CDC). National Center for Health Statistics. WHO growth standards are recommended for use in the U.S. for infants and children 0 to 2 years of age. 2010. Accessed January 25, 2022. https://www.cdc.gov/nccdphp/dnpao/growthcharts/who/downloads/using_who_growth_charts.pdf
69. Centers for Disease Control and Prevention (CDC). CDC's developmental milestones. 2021b. Accessed January 25, 2022. https://www.cdc.gov/ncbddd/actearly/milestones/index.html
70. Gliklich R, Dreyer N, Leavy M, eds. *Registries for evaluating patient outcomes: a user's guide; 4th ed*. Agency for Healthcare Research and Quality (AHRQ); 2020. https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/registries-evaluating-patient-outcomes-4th-edition.pdf.
71. American College of Obstetricians and Gynecologists (ACOG). Committee Opinion No. 700: methods for estimating the due date. *Obstet Gynecol*. 2017;129(5):e150-154.
72. Covington DL, Mates H, Churchill P, Golembesky A, McKain LF. Improving accuracy inenrollment targets for pregnancy registries. *Pharmacoepidemiol Drug Saf*. 2010;19(suppl 1):S71-72.
73. Veley K, Covington DL, Buus R, Chan RL, Churchill P. Sample size calculations for pregnancy registries: improving accuracy. *Pharmacoepidemiol Drug Saf*. 2020;29(3):537-538.
74. Centers for Disease Control and Prevention (CDC). Update on overall prevalence of majorbirth defects – Atlanta, GA,1978-2005. *MMWR Morb Mortal Wkly Rep*. 2008;57(1):1-5.

75. Ananth CV, Keyes KM, Wapner RJ. Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis. *BMJ*. 2013;347:f6564. doi:10.1136/bmj.f6564
76. Butwick AJ, Druzin ML, Shaw GM, Guo N. Evaluation of US State-Level Variation in Hypertensive Disorders of Pregnancy. *JAMA Netw Open*. 2020;3(10):e2018741. doi:10.1001/jamanetworkopen.2020.18741
77. Martin JA, Hamilton BE, Osterman MJK, Driscoll AK. Births: Final Data for 2019. *Natl Vital Stat Rep*. 2021;70(2):1-51.
78. Wu P, Velez Edwards DR, Gorrindo P, et al. Association between First Trimester Antidepressant Use and Risk of Spontaneous Abortion. *Pharmacotherapy*. 2019;39(9):889-898. doi:10.1002/phar.2308
79. MacDorman MF, Gregory EC. Fetal and Perinatal Mortality: United States, 2013. *Natl Vital Stat Rep*. 2015;64(8):1-24.
80. Jatlaoui TC, Eckhaus L, Mandel MG, et al. Abortion surveillance – United States, 2016. *MMWR Surveill Summ*. 2019;68(11):1-41.
81. Rosenberg SA, Zhang D, Robinson CC. Prevalence of developmental delays and participation in early intervention services for young children. *Pediatrics*. 2008;121(6):e1503-1509. doi:10.1542/peds.2007-1680
82. Mogos MF, Piano MR, McFarlin BL, Salemi JL, Liese KL, Briller JE. Heart failure in pregnant women: a concern across the pregnancy continuum. *Circulation: Heart Failure*. 2018;11(1):e004005.
83. Harper MA, Meyer RE, Berg CJ. Peripartum cardiomyopathy: population-based birth prevalence and 7-year mortality. *Obstet Gynecol*. 2012;120(5):1013-1019. doi:10.1097/aog.0b013e31826e46a1
84. American College of Obstetricians and Gynecologists (ACOG). Practice Bulletin No. 153: nausea and vomiting of pregnancy. *Obstet Gynecol*. 2015;126:e12-e24.
85. Deputy NP, Sharma AJ, Kim SY. Gestational Weight Gain — United States, 2012 and 2013. *Morbidity and Mortality Weekly Report*. 2015;64(43):1215-1220.
86. Hocquette A, Durox M, Wood R, et al. International versus national growth charts for identifying small and large-for-gestational age newborns: A population-based study in 15 European countries. *Lancet Reg Health Eur*. 2021;8:100167. doi:10.1016/j.lanepe.2021.100167
87. Eckhardt CL, Eng H, Dills JL, Wisner KL. The prevalence of rapid weight gain in infancy differs by the growth reference and age interval used for evaluation. *Ann Hum Biol*. 2016;43(1):85-90. doi:10.3109/03014460.2014.1002533
88. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of Obesity and Severe Obesity Among Adults: United States, 2017-2018. *NCHS Data Brief*. 2020;(360):1-8.
89. Janssen F, Bardoutsos A, Vidra N. Obesity Prevalence in the Long-Term Future in 18 European Countries and in the USA. *Obes Facts*. 2020;13(5):514-527. doi:10.1159/000511023
90. Schienkiewitz A, Mensink GBM, Kuhnert R, Lange C. Overweight and obesity among adults in Germany. *J Health Monit*. 2017;2(2):20-27. doi:10.17886/RKI-GBE-2017-038
91. MacEwan J, Kan H, Chiu K, Poon JL, Shinde S, Ahmad NN. Antiobesity Medication Use Among Overweight and Obese Adults in the United States: 2015-2018. *Endocr Pract*. 2021;27(11):1139-1148. doi:10.1016/j.eprac.2021.07.004
92. CIA.gov. Birth rate. Accessed April 2024. https://www.cia.gov/the-world-factbook/field/birth-rate/country-comparison/

93. Feldkamp ML, Botto LD, Carey JC. Reflections on the etiology of structural birth defects: Established teratogens and risk factors. *Birth Defects Res A Clin Mol Teratol*. 2015;103(8):652-655. doi:10.1002/bdra.23392
94. Polifka JE, Friedman JM. Medical genetics: 1. Clinical teratology in the age of genomics. *CMAJ*. 2002;167(3):265-273.
95. TERIS: the Teratogen Information System. 2020. Accessed January 25, 2022. https://deohs.washington.edu/teris/
96. Zomerdijk IM, Ruiter R, Houweling LM, Herings RM, Straus SM, Stricker BH. Dispensing of potentially teratogenic drugs before conception and during pregnancy: a population-based study. *BJOG*. 2015;122(8):1119-1129. doi:10.1111/1471-0528.13128
97. Mason CA, Kirby RS, Sever LE, Langlois PH. Prevalence is the preferred measure of frequency of birth defects. *Birth Defects Res A Clin Mol Teratol*. 2005;73(10):690-692. doi:10.1002/bdra.20211
98. Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol*. 2004;159(7):702-706. https://doi.org/10.1093/aje/kwh090
99. Robins JM RA, Zhao LP. Estimation of regression coefficients when some regressors are notalways observed. J Am Stat Assoc. 1994;89(427):846-66.
100. Robins JM RA. Semiparametric efficiency in multivariate regression models with missingdata. J Am Stat Assoc. 1995;90(429):122-9.
101. Scharfstein DO RA, Robins JM. Adjusting for nonignorable drop-out using semiparametric nonresponsemodels. J Am Stat Assoc. 1999;94(448):1096-1120.
102. Chesnaye NC, Stel VS, Tripepi G, et al. An introduction to inverse probability of treatment weighting in observational research. *Clin Kidney J*. 2022;15(1):14-20. doi:10.1093/ckj/sfab158
103. Li F, Thomas LE, Li F. Addressing Extreme Propensity Scores via the Overlap Weights. *Am J Epidemiol*. 2019;188(1):250-257. doi:10.1093/aje/kwy201
104. Segalas C, Leyrat C, Carpenter JR, Williamson E. Propensity score matching after multiple imputation when a confounder has missing data. *Stat Med*. 2023;42(7):1082-1095. doi:10.1002/sim.9658
105. Bennett DA. How can I deal with missing data in my study? *Aust N Z J Public Health*. 2001;25(5):464-469.
106. Bell BA, Ferron JM, Kromrey JD. Cluster size in multilevel models: The impact of sparse data structures on point and interval estimates in two-level models. *JSM Proceedings, section on survey research methods*. 2008:1122-1129.
107. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav Res*. 2011;46(3):399-424. doi:10.1080/00273171.2011.568786
108. Gaster T, Eggertsen CM, Stovring H, Ehrenstein V, Petersen I. Quantifying the impact of unmeasured confounding in observational studies with the E value. *BMJ Med*. 2023;2(1):e000366. doi:10.1136/bmjmed-2022-000366
109. Kennedy DL, Uhl K, Kweder SL. Pregnancy exposure registries. *Pharmacoepidemiol Drug Saf*. 2004;27(4):215-228.
110. Guidelines for Good Pharmacoepidemiology Practices (GPP). 2015. Accessed January 25, 2022. www.pharmacoepi.org/resources/policies/guidelines-08027/

Annex 1. List of Standalone Documents

No.	Document Reference No.	Title
1	VV-PVG-124308	Responsible Parties Contact List
2	VV-PVG-127799	Drugs of Interest for Cohort Eligibility
3	VV-PVG-127798	List of Known Teratogens

Abbreviation: No. = number.

Annex 2. ENCePP Checklist for Study Protocols

Study title: Tirzepatide Pregnancy Registry: A Multi-Country Registry-Based Observational Study to Assess Maternal, Fetal, and Infant Outcomes Following Treatment with Tirzepatide for Weight Management During Pregnancy

EU PAS Register® number: EUPAS1000000517

Study reference number (if applicable): I8F-MC-B016

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

Comments:

[2] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[3] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7.1, 8, 9.5, 9.11
2.1.2 The objective(s) of the study?	☒	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary, or combined data collection?	☒	☐	☐	10.1
3.3 Does the protocol specify measures of occurrence? (e.g. rate, risk, prevalence)	☒	☐	☐	8
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.11.2
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	10

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.5
4.2 Is the planned study population defined in terms of: 4.2.1 Study time period 4.2.2 Age and sex 4.2.3 Country of origin 4.2.4 Disease/indication 4.2.5 Duration of follow-up	☒ ☒ ☒ ☒ ☒	☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐	6, 9.5, 9.1,
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.5.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.7.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.7.1
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.7.1

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.7.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.7.1
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	8, 9.5.2

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.2, 9.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.7.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.7.3
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.5.2, 9.11.2.4, 9.11.2.7, 9.13
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.13
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.7.1

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.11.2.6, 9.11.2.7

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.8
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.8

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.8
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.8
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.8
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.8
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.7.3
9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.11.2

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.9
10.3 Are descriptive analyses included?	☒	☐	☐	9.11.2
10.4 Are stratified analyses included?	☒	☐	☐	9.11.2.5
10.5 Does the plan describe methods for analytical control of confounding?	☒	☐	☐	9.11.2.4
10.6 Does the plan describe methods for analytical control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.11.2.8
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.11.2.7

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.10
11.2 Are methods of quality assurance described?	☒	☐	☐	9.12
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.20

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of: 12.1.1 Selection bias? 12.1.2 Information bias? 12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒ ☒ ☒	☐ ☐ ☐	☐ ☐ ☐	9.13
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.9

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/Institutional Review Board been described?	☒	☐	☐	9.15, 9.18
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9.15

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	11
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	11

Comments:

Name of the main author of the protocol: PPD, Part of Thermo Fisher Scientific

Date: See Page 1 of the protocol for approval date

Signature: _____

Annex 3. Birth Defects Code List

MACDP Birth Defects Code List:

https://www.cdc.gov/ncbddd/birthdefects/documents/MACDP-Code-List-Updated-Nov-2023_Rev_Website2-508c.xlsx

CDC List of Minor Congenital Anomalies:

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

EUROCAT Coding and Classification:

https://eu-rd-platform.jrc.ec.europa.eu/system/files/public/eurocat/Guide_1.5_Chapter_3.5.pdf