TITLE PAGE

Division: Global Medical, Pharma R&D
Information Type: Epidemiology Study Protocol

Title:	Zanamivir 10 mg/ml solution for infusion pregnancy registry: an observational study of the safety of zanamivir 10 mg/ml solution for infusion exposure in pregnant women with complicated influenza and their offspring.

Compound Number:	GR121167
Development Phase	Phase IV
Effective Date:	23-JUN-2020
Subject:	Safety of zanamivir 10 mg/mL solution for infusion in pregnancy
Author(s):	PPD (GSK), PPD (GSK), PPD

PASS information

Title	Zanamivir 10 mg/ml solution for infusion pregnancy registry: an observational study of the safety of zanamivir 10 mg/ml solution for infusion exposure in pregnant women with complicated influenza and their offspring.
Protocol version identifier	D-2017N341239_00
Date of last version of protocol	Not applicable
EU PAS (ENCEPP) register number	Study to be registered
Active substance	Zanamivir
Medicinal product	Zanamivir 10 mg/mL solution for infusion
Product reference	EMEA/H/C/4102
Procedure number	Not applicable
Marketing authorisation holder(s)	GlaxoSmithKline Trading Services Ltd Currabinny Carrigaline County Cork Ireland
Joint PASS	No
Research question and objectives	To evaluate pregnancy outcomes among women with complicated influenza exposed to zanamivir 10 mg/mL solution for infusion at any time during pregnancy including: 1) maternal death, 2) pregnancy outcomes including spontaneous losses in clinically recognised pregnancies, induced abortions, stillbirths and live births and 3) birth outcomes including low birth weight, small for gestational age, prematurity, congenital malformations and neonatal death.
Country(-ies) of study	Member states of the European Union, United Kingdom, Norway and Iceland
Author	PPD (GSK), PPD (GSK), PPD

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	GlaxoSmithKline Trading Services Ltd Currabinny Carrigaline County Cork Ireland
MAH contact person	PPD

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SPONSOR INFORMATION PAGE

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline affiliate company (or designee). Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission.

Sponsor Medical Monitor Contact Information: To be determined

Sponsor Serious Adverse Events (SAE) Contact Information: To be determined

Regulatory Agency Identifying Number(s):

Agency Product Number - EMEA/H/C/4102

Product Licence number - EU/1/18/1349/001

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:

_____

Investigator Signature	Date

SCIENTIFIC ADVISORY COMMITTEE

The Scientific Advisory Committee will be convened to provide an independent review of registry data and will include specialists from appropriate fields such as obstetrics, paediatrics, infectious diseases, clinical research, genetics, epidemiology, and teratology from academic institutions, private practice, and/or government agencies.

The composition of the Advisory Committee remains to be determined.

1. LIST OF ABBREVIATIONS

AE	Adverse Event
CDC	Centers for Disease Control
CEDD	Corrected Estimated Date of Delivery
CFR	Code of Federal Regulations
CRO	Contract Research Organization
CUP	Compassionate Use Program
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDD	Estimated Date of Delivery
EMA	European Medicines Agency
EU	European Union
EU PASS	European Union Post Authorization Safety Study
EUROCAT	European Registry of Congenital Malformation and Twin Registries
GPP	Good Pharmacoepidemiology Practice
GSK	GlaxoSmithKline
HCP	HealthCare Provider
HDU	High Dependency Unit
IAB	Induced Abortion
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive Care Unit
IHD	Individual Human Data
INOSS	International Obstetric Surveillance System
IRM	Individual Rights Management
IV	Intravenous
LBW	Low birthweight
LMP	Last Menstrual Period
MACDP	Metropolitan Atlanta Congenital Defect Program
MCMs	Major Congenital Malformations
NAI	Neuraminidase Inhibitors
OXON	Oxon Epidemiology
REVA-SRLF	REseau de recherche en Ventilation Artificielle – Societe Reanimation de Langue Francaise
SAB	Spontaneous Abortion
SAC	Scientific Advisory Committee
SAP	Statistical Analysis Plan

SGA	Small for Gestational Age
SOP	Standard Operating Procedure
STD	Standard
sPVP	Study Specific PharmacoVigilance Plan
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
UK	United Kingdom
UKOSS	United Kingdom Obstetric Surveillance System

Trademark Information

Trademarks of the GlaxoSmithKline group of companies	Trademarks of non GlaxoSmithKline group of companies
DECTOVA	PASS

2. RESPONSIBLE PARTIES

2.1. Main Author(s) of the Protocol

PPD

2.2. Principal Investigator

PPD

Spain

2.3. Coordinating Investigator(s)

PPD

Additional investigators from the INOSS network to be identified

2.4. Advisory Committee

The Scientific Advisory Committee will be convened to provide an independent review of registry data and will include specialists from appropriate fields such as obstetrics, paediatrics, infectious diseases, clinical research, genetics, epidemiology, and teratology from academic institutions, private practice, and/or government agencies.

The composition of the Advisory Committee remains to be determined.

3. ABSTRACT

Title

Zanamivir 10 mg/ml solution for infusion pregnancy registry: an observational study of the safety of zanamivir 10 mg/ml solution for infusion exposure in pregnant women with complicated influenza and their offspring.

Rationale and Background

Pregnant women are a group at risk of increased influenza related morbidity and mortality.

GlaxoSmithKline (GSK) has been awarded a marketing authorisation for zanamivir 10 mg/mL solution for infusion (hereafter referred to as intravenous (IV) zanamivir) under exceptional circumstances, pursuant to article 14 (8) of Regulation (EC) no 726/2004. The indication is:

Dectova is indicated for the treatment of complicated and potentially life-threatening influenza A or B virus infection in adult and paediatric patients (aged ≥6 months) when:

- *The patient's influenza virus is known or suspected to be resistant to anti-influenza medicinal products other than zanamivir, and/or*
- *Other anti-viral medicinal products for treatment of influenza, including inhaled zanamivir, are not suitable for the individual patient.*

Dectova should be used in accordance with official guidance.

This prospective observational study aims to evaluate pregnancy outcomes among women exposed to IV zanamivir during pregnancy.

Research Question and Objectives

The objective of the pregnancy registry is to evaluate pregnancy outcomes among women exposed to IV zanamivir at any time during pregnancy. Outcomes of interest will include: 1) maternal death, 2) pregnancy outcomes including spontaneous losses in clinically recognised pregnancies, induced abortions (IABs), stillbirths and live births and 3) birth outcomes including low birth weight (LBW), small for gestational age (SGA), prematurity, congenital malformations and neonatal death.

This registry is primarily descriptive and designed to detect potential safety signals rather than test hypotheses.

Study Design

This pregnancy registry will be a multi-centre, prospective observational cohort study using the United Kingdom Obstetric Surveillance System (UKOSS) and International Obstetric Surveillance System (INOSS) as the principal sources to identify IV zanamivir exposed pregnancies. The registry will collect data directly from healthcare providers (HCPs) based on information that is routinely documented in the participant's medical record as part of usual clinical care. Data will be collected at enrolment as close as possible to the time of exposure to IV zanamivir in pregnancy and at pregnancy outcome (delivery or early termination) with follow up out to three months after delivery to increase birth outcome ascertainment in the infant.

Population

Pregnant women with complicated influenza who have been exposed to at least one dose of IV zanamivir during pregnancy will be eligible to participate in the registry. Minimum criteria for enrolment will be the following:

- Sufficient evidence to confirm exposure to IV zanamivir during pregnancy based on information from the reporter.
- Sufficient information to determine whether the pregnancy is prospectively or retrospectively recorded (i.e., whether the outcome of pregnancy was known at the time of enrolment).
- Date of enrolment into the pregnancy registry.
- Treating hospital contact information to allow for follow-up.
- Women aged >18 years at time of enrolment.

Identification largely via the UKOSS and INOSS systems is proposed, followed by enrolment study staff. De-identified data provided by HCPs under the waiver of informed consent provision will also be collected where allowed under local country laws.

Variables

The exposure of interest will be IV zanamivir during pregnancy.

Outcomes of interest will include: 1) maternal death, 2) pregnancy outcomes including spontaneous losses in clinically recognised pregnancies, induced abortions, stillbirths and live births and 3) birth outcomes including low birth weight, small for gestational age, prematurity, congenital malformations and neonatal death.

Covariates of interest will include: maternal age and ethnicity; prenatal data including estimated date of delivery (EDD); prenatal tests, obstetric history, current pregnancy complications, clinical details of influenza episode, other co-morbidities, concomitant medication exposure and smoking use during pregnancy as well as infant gender and multiple gestations.

Data Sources

Appropriate members of the women's health care team will serve as data reporters to the registry based on information in the medical record. Only data noted as part of routine care will be collected. The registry will perform targeted follow-up to collect additional data on events and outcomes of interest as needed. Congenital malformations will be reviewed by a clinical genetics/teratology specialist on the Scientific Advisory Committee overseeing interpretation of data from the registry.

Study Size

For a range of pregnancy outcomes of interest, sample size calculations considered the number of live births needed to detect the associated effect sizes using a binomial distribution with 80% power and a 1-sided Type I (false positive) error rate of 5%. Assuming prevalence values in the reference population of 2% (major malformations) and 7.6% (preterm births), 100 exposed live births will be sufficient to detect a 4-fold increase in the risk of major congenital malformations and a 2-fold increase in the risk of pre-term births, relative to the reference-population prevalence.

Data Analysis

Demographic and baseline characteristics will be summarized with simple descriptive statistics and data listings for the evaluable population of pregnant women and live births.

Point estimates and 95% confidence intervals will be calculated using the binomial distribution for prevalence estimates of maternal death and pregnancy outcomes among pregnant women exposed to at least one dose of IV zanamivir and for birth outcomes including preterm birth, LBW, SGA and neonatal deaths among their exposed live births. Prevalence estimates for congenital malformations will consider congenital malformations identified in both live births and foetal deaths. For each prevalence estimate, both 1-sided and 2-sided 95% confidence intervals will be calculated and reported. Outcome prevalence estimates will be presented overall and stratified according to the trimester of IV zanamivir exposure.

The registry is primarily descriptive aiming to determine a signal for substantial increase in risk. Therefore, comparisons will be descriptive. Primary comparisons will be against external comparators reflecting population-based surveillance of pregnancy outcomes and literature-based disease cohorts. If it is feasible, descriptive comparisons between the registry and an appropriate internal comparator will be examined.

Milestones

The registry will be implemented following the granting of the marketing authorisation for IV zanamivir and before the start of the first northern hemisphere influenza season following that grant. The registry will be opened in countries within the European Union (EU), United Kingdom (UK), Norway and Iceland. At present 100-150 exposures during pregnancy to IV zanamivir are proposed to be sufficient to detect 2-4-fold increases in the risk of adverse pregnancy outcomes of interest and therefore sufficient to detect a signal for substantial increase in risk. The prevalence of exposure to IV zanamivir is likely to vary across influenza seasons influenced by factors such as the underlying pathogenicity and resistance profiles of circulating virus strains. Accordingly, an update report will be filed with the EMA each year, providing details of the number of treated patients enrolled and guidance on the likely study end date.

4. AMENDMENTS AND UPDATES

Amendment or update no.	Date	Section of study protocol	Amendment or update
1	23-JUN-2020	8.4 Data source 8.7 Data Analysis, sub-section Analysis Population	Clarified that additional de-identified data, collected by HCPs to supplement the primary analysis population collected through the pregnancy study, can include the minimal dataset collected under informed consent waiver from the UKOSS/INOSS network. This will enable access to a minimal set of data on women exposed to IV zanamivir from UKOSS/INOSS but who do not consent to participate in the current study.

5. MILESTONES

Milestone	**Planned date**
Start of data collection	Before the end of the first northern hemisphere influenza season following marketing authorisation.
End of data collection	An update report will be filed with the EMA each year, providing details of the number of treated patients enrolled and guidance on the likely study end date.
Final report of study results	Within 6 months after eCRF completion for last subject

6. RATIONALE AND BACKGROUND

6.1. Background

Pregnant women are recognised as a group at increased risk of severe disease and death secondary to influenza infection mainly based on observations of excess influenza-related mortality in pregnant women during historical and recent pandemics [Harris, 1919; Freeman, 1959, Siston, 2010] and higher rates of influenza-related morbidity requiring hospitalisation during seasonal epidemics [Dodds, 2007; Neuzil, 1998; Mertz, 2013]. For example, in the United States, pregnant women had a 4-fold greater risk of hospitalisation due to A/H1N1 infections compared to the general population in the pandemic of 2009/2010 [Jamieson, 2009]. In addition, influenza and fever may increase the risk of adverse pregnancy outcomes [Meijer, 2015; Siston, 2010; Mosby, 2011; Haberg, 2013]. These effects were confirmed in the United Kingdom where risks of perinatal mortality, as well as preterm birth, were 4-fold greater in mothers infected with A/H1N1 during pregnancy [Pierce, 2011]. Furthermore, a recent systematic review and meta-analysis reported an association between severe A/H1N1 disease and preterm birth and foetal death [Fell, 2017].

In the European Union, oseltamivir, taken orally, zanamivir which is inhaled, peramivir which is a solution to be diluted and used as an infusion and now intravenous zanamivir, are the four approved neuraminidase inhibitors (NAIs). Early treatment of influenza with oseltamivir has been associated with a reduced risk of severe infection and of admission to intensive care units (ICU) for pregnant women [Meijer, 2015; Delgado-Rodriguez, 2012]. Prior to the last influenza pandemic of 2009 there were few data on NAI safety in pregnancy. A recent European study of population-based registers from Denmark, Norway and Sweden and France captured data reflecting increased uptake of NAIs in pregnant women following the 2009 pandemic. Data from prescription registers, capturing NAI exposure during pregnancy, were linked to birth registers capturing information on pregnancy outcomes. Exposure to NAIs during pregnancy was not associated with increased risks of neonatal outcomes including LBW, SGA, preterm birth, stillbirth, neonatal death and neonatal morbidity. First trimester exposure was not associated with an increased risk of congenital malformations [Graner, 2017]. Although 74% of the NAIs exposures during pregnancy were to oseltamivir, data specific for zanamivir (including 321 first trimester zanamivir exposures) were not reported separately. Several additional observational studies of inhaled zanamivir exposure in pregnancy, with sample sizes ranging from 50 to 180 inhaled zanamivir exposures during any trimester of pregnancy, have failed to report a significant increase in adverse pregnancy outcomes [Walker, 2014; Saito, 2013; Dunstan, 2014].

Pre-clinical studies in rats and rabbits have failed to identify increased risks for malformations, maternal toxicity, or embryotoxicity following intravenous (IV) administration of zanamivir at doses up to 90 mg/kg/day. A further embryofoetal development study following subcutaneous administration of zanamivir at doses of up to 80 mg/kg, 3 times daily (240 mg/kg/day), observed an increase in the incidence rates of a variety of minor skeleton alterations and variants in the offspring at systemic exposure greater than approximately 3 times the human exposure at the clinical intravenous dose (600 mg twice daily). In most instances, the individual incidence rate of each skeletal alteration or variant remained within the background rates of the historical occurrence in the strain studied.

No randomised controlled trials have studied the effect of inhaled and IV zanamivir exposure on pregnancy outcomes.

Due to limited treatment options, antiviral drug resistance remains a public health concern, and alternative treatments to oseltamivir are needed in case of widespread resistance. Although orally inhaled zanamivir has been shown to be less prone to drug resistance, there is also an unmet medical need for patients who are unable to take oral or actively inhaled medications; e.g. children, patients who are not awake or strong enough to inhale, patients with underlying lung disease, or patients on mechanical ventilation, for which there are limited treatment options. GlaxoSmithKline (GSK) initiated the clinical development of an intravenous formulation of zanamivir (IV zanamivir) in response to the 2009 influenza A/H1N1 pandemic. A global compassionate use program (CUP) was initiated in May 2009 at the onset of the A/H1N1 influenza pandemic to provide IV zanamivir on a named-patient basis to seriously ill patients with suspected or confirmed influenza for whom approved anti-influenza drugs were not effective or not feasible. IV

zanamivir is administered as a 600mg dose twice daily that is infused over a 30-minute period. The recommended course is for 5 days, but can be extended depending on disease severity and progress

GSK has gained approval under exceptional circumstances for IV zanamivir in the EU. The indication is for the treatment of complicated and potentially life-threatening influenza A or B virus infection in adult and paediatric patients (aged ≥6 months) when:

- The patient's influenza virus is known or suspected to be resistant to anti-influenza medicinal products other than zanamivir, and/or
- Other anti-viral medicinal products for treatment of influenza, including inhaled zanamivir, are not suitable for the individual patient.

Dectova should be used in accordance with official guidance.

Given that pregnant women are a group at high risk of influenza related morbidity and mortality, exposure to IV zanamivir in pregnancy is likely.

6.2. Rationale

This prospective observational study aims to evaluate pregnancy outcomes among women hospitalised with complicated influenza and exposed to IV zanamivir during pregnancy in the European Union, UK, Iceland and Norway.

7. RESEARCH QUESTION AND OBJECTIVE(S)

The objective of the Zanamivir 10 mg/mL solution for infusion pregnancy registry is to evaluate pregnancy outcomes among women exposed to IV zanamivir at any time during pregnancy. Outcomes of interest will include: 1) maternal outcome of maternal death, 2) pregnancy outcomes including spontaneous losses in clinically recognised pregnancies, IABs, stillbirths and live births and 3) birth outcomes including low birth weight, small for gestational age, prematurity, congenital malformations and neonatal death.

This registry is primarily descriptive and designed to detect potential safety signals rather than test hypotheses.

8. RESEARCH METHODS

8.1. Study Design

The IV zanamivir pregnancy registry is a prospective, observational study of pregnant women treated with IV zanamivir at any time during pregnancy. It will be based on exposures during pregnancy reported through the UKOSS and the INOSS as the principal sources for exposure identification and will be strictly observational; the schedule of healthcare visits and encounters and all treatment regimens will be determined by the treating HCP. The registry will collect data that are routinely documented in the patient's medical record as part of usual care.

8.2. Study Population and Setting

Once initiated, pregnant women exposed to IV zanamivir in the European Union, United Kingdom (UK), Iceland and Norway identified through UKOSS and INOSS will be eligible to be enrolled in the pregnancy registry.

UKOSS is a well-established national system to collect information about severe maternal morbidity through more than 700 collaborating clinicians in all 198 hospitals with consultant-led maternity units throughout the UK (see www.npeu.ox.ac.uk/ukoss for further information). All hospitals in the UK with a consultant-led maternity unit collaborate in UKOSS, and thus it is an ideal mechanism to maximise identification of exposures of IV Zanamivir in women hospitalised with influenza across the UK, as well as to collect information on their management and outcomes. This system has been demonstrated to be able to rapidly collect information to inform policy and guidance in a previous pandemic [ANZIC, 2010; Jamieson, 2009]. INOSS is the equivalent population-based network across other European countries. INOSS networks have similar but varying set-ups, which will be used and adapted for this study. The main addition to the existing UKOSS and INOSS structures will be with the addition of an infant follow-up at 3 months and the ability to follow regulatory pharmacovigilance reporting procedures enabled by OXON.

The data collection process for each participant will begin at enrolment (during pregnancy) with follow-up to occur at pregnancy outcome (delivery or early termination) and out to 3 months post-delivery for live births to capture maternal deaths, neonatal deaths and to increase ascertainment of congenital anomalies.

The study population will include pregnant women in the European Union, UK, Iceland and Norway hospitalised with complicated influenza who received at least one dose of IV zanamivir at any time during pregnancy and are identified through the UKOSS and INOSS networks. IV zanamivir should be used during pregnancy only if clearly needed, and exposure during pregnancy may be expected because pregnant women represent a group at risk of hospitalisation with complicated influenza for which an IV formulation may be needed.

The minimum criteria required for enrolment into the registry will include:

- Sufficient evidence to confirm that exposure to IV zanamivir occurred at any time during pregnancy based on information from the reporter.
- Sufficient information to determine whether the pregnancy is prospectively or retrospectively recorded (i.e., whether the outcome of pregnancy was known at the time of first contact with the registry).
- Date of enrolment into the registry.
- Treating hospital contact information to allow for follow-up.
- Women aged >18 years at time of enrolment.

If it cannot be ascertained to which anti-influenza medication the woman was exposed, an unknown exposure cohort will be established and analysed separately. Pregnancy exposures ascertained prospectively (before the outcome of pregnancy) will initially be analysed separately from those ascertained retrospectively.

Patients will be identified through UKOSS and INOSS networks and data collection will be coordinated through study staff and the study contract research organization (CRO) (OXON).
It will also be possible to supplement study data using de-identified data provided by HCPs under the waiver of informed consent provision. This could include exposures and outcomes identified through anonymised healthcare electronic medical record data sources.

All study information materials will be in accordance with the approved Prescribing Information Documentation in the EU.

Reference Groups
Given the inherent difficulties in identifying a comparison group within a pregnancy registry [Covington, 2009], several different methods may be used to review the data for safety signals. As described below, background prevalence estimates from external surveillance sources and estimates from published literature will be the primary comparators. To the extent possible, comparator prevalence estimates will be age-adjusted to reflect the age distribution of the pregnancy registry population and will also consider disease severity.

An untreated disease comparator group is unlikely to be feasible to recruit within the registry as national and international guidelines are to treat pregnant women with influenza antivirals due to an increased risk of morbidity associated with influenza. As other NAIs approved in the European Union are not specifically indicated for the treatment of complicated influenza, appropriate comparators by disease severity are also likely to be difficult to identify outside of surveillance programs and the literature. Comparisons between inhaled and IV zanamivir exposures will also be inappropriate due to difference in the underlying severity of disease associated with mode of treatment administration.

As treatment options may change over time, potential comparators will be assessed on a regular basis and if possible, a concurrent comparator group of IV zanamivir unexposed pregnant women with complicated influenza will also be recruited into the registry.

Background Prevalence Estimates of Pregnancy Outcomes
Background prevalence estimates of pregnancy outcomes in the general population, such as premature birth and LBW, are readily available from national vital statistics or publications in the scientific literature [Office for National Statistics, 2015]. Rates for a range of countries participating in the registry will be reviewed so that variation in background rates can be considered.

Background Prevalence Estimates of Major Congenital Malformations (MCMs)
Published prevalence estimates of MCMs are available from the European Registry of Congenital Malformation and Twin Registries (EUROCAT) which is an ongoing population-based birth defects surveillance program across Europe [EUROCAT, 2017]. EUROCAT is a European network of population-based registries covering 29% of the European population. It started in 1979 and covers 1.5 million births per year in Europe. Its primary objectives are to provide essential epidemiological information on congenital

malformations and to act as an information and resource centre to individuals and public health professionals.

As EUROCAT is primarily a passive surveillance system, background prevalence estimates from active surveillance approaches will also be considered. The Centre for Disease Control and Prevention's (CDC) Metropolitan Atlanta Congenital Defects Program (MACDP) actively searches for congenital malformations among the 50,000 annual births to residents of metropolitan Atlanta's 5 counties and abstracts medical records at all Atlanta obstetric hospitals, paediatric referral hospitals, genetics laboratories, and vital records [Correa-Villasenor, 2003]. MACDP data have been used as the comparator cohort in examinations of congenital malformations for other pregnancy registries despite differences in geographic focus (for example with other GlaxoSmithKline products including acyclovir, sumatriptan, lamotrigine, and zidovudine) [Honein, 1999]. The most recent CDC MACDP 5-year major malformation prevalence was 2.78% (6,945 cases with birth defects/249,999 live births) from 1999 to 2003.

In the absence of appropriate influenza disease-based comparators these will form the primary population-based comparator groups.

Background Prevalence Estimates from Literature or Other Studies
The registry will identify other appropriate comparison groups through research of the literature and other sources, such as other pregnancy registries or observational studies. Particular attention will be paid to identify appropriate disease-based comparators in the literature, specifically pregnant women with influenza.

Concurrent comparator of untreated influenza pregnant women
Influenza itself is associated with adverse pregnancy outcomes and increased maternal influenza related mortality and morbidity. General population comparator groups will therefore not represent the same baseline risk of adverse pregnancy outcomes as women with influenza exposed to IV zanamivir. As treatment options may change over time, potential comparators will be assessed on a regular basis to assess if it will be feasible to enrol a disease comparator group that is unexposed to treatment or unexposed to IV zanamivir with similar underlying disease severity (complicated influenza).

8.3. Variables

Key clinical data that will be collected for this study are described below.

8.3.1. Exposure definitions

This pregnancy registry is strictly observational and confirmed exposure to IV zanamivir at any time during pregnancy is a condition of enrolment. The exposure of interest is exposure to at least one dose of IV zanamivir during pregnancy. If the anti-influenza medication to which the woman was exposed cannot be ascertained, an unknown exposure cohort will be established and analysed separately.

Data to be collected include the date of medication exposure and dose.

8.3.2. Outcome definitions

There are three groups of outcomes of interest:

Maternal outcomes

- Maternal death during pregnancy and up to 42 days after delivery.

Pregnancy outcomes

- Live birth defined as an infant born alive.
- Spontaneous abortion (SAB) in clinically recognized pregnancies defined as foetal death or expulsion of products of conception prior to 20 weeks' gestation, or if gestational age is unknown, weighing less than 500g.
- Stillbirths defined as a foetal death occurring at 20 weeks' gestation or greater, or if gestational age is unknown, a foetus weighing 500 g or more.
- IAB defined as voluntary interruption of pregnancy, including pregnancy termination that occurs electively, to preserve maternal health, or due to foetal abnormalities.

Birth outcomes

- Prematurity defined as an infant born at gestational age <37 weeks.
- SGA defined as an infant born with a birth weight less than the 10th centile for the corresponding gestational age.
- LBW defined as an infant whose birth weight is <2500 g.
- Neonatal death defined as death of the infant within 28 days of birth.
- Major congenital malformation (MCM) defined according to EUROCAT criteria
- EUROCAT includes all major structural malformations and chromosomal malformations. Minor anomalies are excluded (as defined in Section 3.2 of the coding guide) and cases with more than one malformation type are only counted once for the calculation of overall malformation prevalence.

  Maternal and infant follow up is proposed to 3 months after birth. Longer term follow-up is not proposed as there are no pre-clinical or clinical data to suggest a signal for developmental delay. Hence, it is impossible to determine an appropriate longer term follow up period which differs substantially according to the type of developmental adverse outcome of interest. As the majority of major malformations are detected at birth, a three month follow up period is deemed adequate to maximize capture of major malformations.

8.3.3. Confounders and effect modifiers

Additional data will be collected as follows:

***Maternal characteristics*:** Age, ethnicity, country.

Prenatal data: Last menstrual period (LMP), EDD, corrected estimated date of delivery (CEDD).

Prenatal tests: Name of test, date of test, result.

Obstetrical history: Previous pregnancies: live births, stillbirths, SABs, IABs, births with MCMs and family history of MCMs.

Pregnancy complications including preterm labour, pre-eclampsia and placental abruption.

Concurrent medical conditions influenza: including details of influenza episode such as length of hospital stay, HDU/ICU stay (and length of stay), supplemental oxygen, associated complications of influenza (including bacterial pneumonia, sepsis, myocarditis, encephalitis, acute respiratory distress, respiratory failure, bronchitis).

Concurrent medical conditions other: with emphasis on diabetes, hypertension, asthma and autoimmune conditions.

Concomitant medications and vaccines: Medications of specific interest will include teratogens based on the old FDA classification of medications labelled as category X. Lists of medications associated with teratogenicity will be taken from Briggs, 2009 which is consistent with the list used by the clinical geneticist of the North American Anti-Epileptic Drug Register [Holmes, 2004; Correa-Villasenor, 2003;. Medications will then be classified into strong teratogens (e.g., isotretinoin, thalidomide) and more modest teratogens (e.g., carbamazepine).

Tobacco use

Infant gender and multiple gestations

8.4. Data sources

The current UKOSS/INOSS reporters will serve as data reporters identifying exposures for the registry within the UKOSS and INOSS networks. The registry is strictly observational; the schedule of health care visits and encounters as well as all treatment regimens will be determined by the treating HCP. There will be no additional laboratory tests or assessments required as part of this registry. Only data noted as part of routine care will be collected. Maternal characteristics and outcome data will be provided by research staff, where accessible. To aid follow up, the mother will be asked to consent to medical record release and further contact to facilitate pregnancy and infant follow up.

Additionally, the teratologist/geneticist on the scientific advisory committee (SAC) will provide an opinion regarding the possible temporal association of the IV zanamivir

exposure to the development of any observed congenital malformations. If additional information is needed to aid in classification or temporality assessment, the teratologist will request additional information using a targeted follow up process. The SAC will meet periodically to review the data including a discussion of the MCM cases and their classification and temporality with the teratologist and to reach a consensus on the coding and classification of MCMs and other primary endpoints. Healthcare providers may also report de-identified data to the registry. This could include exposures and outcomes identified through anonymised healthcare electronic medical record data sources.

A summary of data that will be collected at specific time points and the source of data are provided in Section 8.6.2.1.

For critical data points, if there are outstanding questions, discrepancies between forms, or missing data, the appropriate reporter will be contacted for clarification. Up to three subsequent attempts, as necessary, will be made at regular intervals (e.g. every two weeks).

Exposure operational definition
At least one dose of IV zanamivir administered at any time during pregnancy will constitute exposure. If the anti-influenza medication to which the woman was exposed cannot be ascertained, an unknown exposure cohort will be established and -analysed separately. Given the short half-life of IV zanamivir (two hours) the start of the exposure window will be conception estimated as described below.

IV zanamivir exposure will be further categorized by earliest trimester of exposure. For this registry, gestational weeks will be estimated from the most reliable EDD as reported by the HCP. If a CEDD is provided by the HCP, it will be used instead. The date of conception will be calculated as the most reliable EDD/CEDD minus 38 weeks. If the EDD is not available or never estimated, the first day of the LMP may be used to estimate gestational age. The second trimester will be considered to begin at week 14 after the date of conception or LMP, and the beginning of the third trimester, at week 28. If there is a discrepancy between gestational age calculated from LMP and reported gestational age, the HCP will be asked to verify the data.

If HCPs provide de-identified data to the registry, they must be able to verify the date of exposure to IV zanamivir. Such data may come from data collected both within and outside of the UKOSS/INOSS network. For example, UKOSS has ethical approval to collect a minimum exposure and outcome dataset on women exposed to new influenza treatments (including IV zanamivir) with a waiver of informed consent. This will enable capture of some data on women who may be exposed to IV zanamivir during hospitalisation with complicated influenza, but do not consent to participate in this study with more complete data collection. A similar situation may arise with other INOSS centres. Other potential de-identified data sources include anonymised healthcare data sources.

Outcome operational definition
All outcome variables will be provided by research staff at sites. They will be asked to describe any MCMs observed in the infant or foetus and will also be asked to report the

gestational age and birth weight. These two variables will be used to calculate preterm birth, LBW, and SGA. Data will be abstracted from medical records. As described above a teratologist/ geneticist will review all reported congenital anomalies and classify them using the EUROCAT system [EUROCAT, 2017].

Operational variable(s) definition
The study staff will provide prenatal data (LMP, EDD, and CEDD), prenatal test data (test, date of test, and result), obstetrical history (previous pregnancies, live births, stillbirths, SABs, IABs, births with MCMs, and family history of MCMs), concurrent medical conditions, concomitant teratogenic medications, and tobacco use during pregnancy through the UKOSS/INOSS system. At pregnancy outcome, research staff will provide pregnancy outcomes data (live birth, stillbirth, SAB, IAB) and infant outcome (gestational age, birth weight, congenital malformations, gender and multiple gestation).

De-identified healthcare data:
If HCPs provide de-identified data to the registry, they will provide required data on maternal characteristics, prenatal data, obstetrical data, and pregnancy outcome data. De-identified data sources may include de-identified data collected under waiver of consent through the UKOSS/INOSS system or de-identified/anonymised healthcare electronic medical record sources where it is possible to identify this exposures and outcomes information.

8.5. Study size

The effect sizes that are expected to be detectable were calculated. The effect size is defined as the ratio of the prevalence in exposed patients, estimated from the study, to the prevalence in the reference population. These calculations were performed using a binomial distribution, a power of 80% and a 1-sided Type 1 (false positive) error rate of 5% [Altman, 1991]. Assuming prevalence values in the reference population of 2% (MCMs) and 7.6% (preterm births), 100 exposed live births will be sufficient to detect a 4-fold increase in the risk of MCMs and a 2-fold increase in the risk of pre-term birth, relative to the reference-population prevalence. The calculations were performed using the software PASS (Version 12.0.2, copyright 1983-2013, NCSS, LCC).

Table 1 Detectable effect size assuming 80% power

Sample size of live births (N)	PTB reference 7.6%[1]	LBW reference 7.0%[1]	MCM reference 2.00%[2]
5	6.45	7.00	24.51
20	4.12	3.69	10.10
50	2. 61	2.83	5.38
100	2.05	2.07	3.90
150	1.85	1.91	2.99

Abbreviations: LBW = low birth weight; MCM = major congenital malformations; PTB = preterm birth.
[1]Prevalence from Office for National Statistics, 2015 [2]Prevalence from EUROCAT, 2017

8.6. Data management

Data for this prospective registry will be managed with an electronic data capture (EDC) platform, which is 21 Code of Federal Regulations (CFR) Part 11 compliant, part of the International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use harmonised tripartate agreement. Research staff will provide data by completing an electronic case report form (eCRF) using the OXON proprietary EDC system after informed consent is obtained from the exposed mother. The EDC will have quality standards and checks pre-programmed.

8.6.1. Data handling conventions

Major congenital malformations will be classified using the EUROCAT coding manual [EUROCAT, 2017]. All malformation classifications will be reviewed by a teratologist/geneticist.

All prenatal exposures to medications will be coded using ATC code dictionaries.

8.6.2. Resourcing needs

The implementation, management and closure of this study will be outsourced to a CRO, OXON Epidemiology. The study will be overseen at GSK by a PhD level Epidemiologist and a Study Delivery Lead.

Biostatistical and methodological issues will be addressed by a senior level statistician with expertise in observational data either from the CRO, or similar, or from within GSK.

8.6.2.1. Timings of Assessment during follow-up

Information requested	Registration provided by HCP	Pregnancy outcome provided by research staff up to 3 months post-delivery	Targeted follow up to collect information not previously obtained, provided by research staff
Maternal contact information, alternate contact information, HCP contact information	X	X[a]	
Maternal characteristics (age,ethnicity, etc.)	X		
Maternal prenatal information (LMP, EDD, CEDD, prenatal test results and timing)	X	X[a]	
Obstetrical history	X		X[b]
Family history of MCMs	X		X[b]

Information requested	Registration provided by HCP	Pregnancy outcome provided by research staff up to 3 months post-delivery	Targeted follow up to collect information not previously obtained, provided by research staff
IV zanamivir exposure information	X	X[a]	
Influenza episode clinical details	X	X[a]	
Pregnancy complications	X	X[a]	
Other Concurrent conditions and concomitant medications, tobacco use during pregnancy	X	X[a]	
Pregnancy status		X	
Outcome information (maternal death, live birth, still birth, SAB, gestational age, birth weight)		X	X[b]
MCM noted and description		X	X[b]

Abbreviations: CEDD = corrected estimated date of deliver; EDD = estimated date of delivery; HCP =health care provider; LMP = last menstrual period; MCM(s) = major congenital malformation(s); Ob =obstetric; SAB = spontaneous abortion.

a Obtain updated information since the previous contact.

b Targeted follow-up is designed to collect addition information (if necessary) to facilitate characterization of the foetal loss, MCMs and/or neonatal death.

8.7. Data analysis

The following approach shall be taken for outcome case management within the registry.

Prospective Registry Reports

The registry will encourage prospective registration, which is defined as registration of a pregnancy exposure prior to knowledge or perceived knowledge of the pregnancy outcome (e.g., structural defect or genetic abnormality noted on a prenatal test).

Prospective reports will be further defined as traditional prospective and pure prospective reports. Traditional prospective reports of pregnancy will include all women who enrol in the registry before the end of pregnancy (live birth, foetal loss, etc), regardless of knowledge of normal or abnormal prenatal test results. Pure prospective reports of pregnancy are a subset of traditional prospective reports and include those where (a) the enrolee did not know at the time of enrolment whether the foetus had adverse outcome such as a malformation, and (b) no prenatal testing was completed prior to enrolment. As the severity of influenza increases with trimester of pregnancy it is likely that most

exposure to IV zanamivir will occur after prenatal screening has occurred. Therefore, in primary analyses, traditional and pure prospective reports will be grouped together.

Data from HCPs that provide de-identified data on all exposed pregnancies in their network will fall into the category of prospective registry reports, as these reports provide objective data on every pregnancy exposure in the network, both positive and negative outcomes. Thus, they avoid the reporting bias inherent in retrospective reporting only after a negative outcome has been noted.

Retrospective Registry Reports

Retrospective reports include subjects for whom the pregnancy outcome has already occurred. Retrospective reports can be biased toward the reporting of more unusual and severe cases and are less likely to be representative of the general population experience than exposures reported prior to knowledge of outcome. Although the exposure can be identified objectives through the UKOSS/INOSS systems, there is still the potential for bias to be introduced if there are delays in the women consenting and between exposure and consent there is additional knowledge of the outcome of the pregnancy. Where possible, the characteristics of prospective and retrospective reports will be compared to assess potential bias. If there is adequate evidence to support lack of bias these prospective and retrospective reports may be combined for analysis, but the initial analysis position will be for retrospective reports not be included in the primary analysis and statistical calculations. Retrospective reports with reported MCMs and/or SABs will be reviewed to aid in detection of early signals and listed in registry reports.

Loss to Follow-up

For a prospective report of pregnancy where follow-up information on the pregnancy outcome (live birth, SAB, etc.) is never obtained or is unavailable, the pregnancy will be considered lost to follow-up. Subjects lost prior to pregnancy outcome will be tallied in the registry reports but not included in the statistical analyses.

Duplicate Registry Reports

With registry reports coming from multiple HCPs, it is important to ensure that each case is counted only once [NBDPN, 2004]. Identification of duplicate reports may be problematic for the anonymously reported de-identified cases where there is no specific identifying information. Reports received by the registry will be reviewed for possible duplicate reporting. On receipt of a registration form, the report will be compared with other reports made by the same reporter or compared with other data (such as age, LMP, EDD, and exposure information) to determine if the same report was received previously. If no duplication is identified, the report will be entered in the database. If a duplicate report is later identified through recall or the systematic check for duplicates, the case reported earliest or the one with the most complete data will be maintained as the valid case and updated with any data from the other report not already captured. The duplicate report will be flagged and designated as “Invalid,” with the reason being noted as “duplicate report.” The criteria for defining a duplicate report will be described ahead of registry operationalisation. Working through the UKOSS/INOSS networks is likely to reduce this problem.

Evaluable Registry Reports

An evaluable report is a subject with data submitted or confirmed by an HCP that contains at least the minimum criteria for a report and is not lost to follow-up. Prospectively reported evaluable subjects with known outcomes will be included in the primary analysis for the registry report. Evaluable retrospective reports will initially be summarized separately in the report (see section on retrospective reports for discussion). Patient-reported data without HCP confirmation will be summarized separately in the report.

Invalid Registry Reports

An invalid registry report is a report for which the minimum data elements are never obtained despite requests for the missing data. If the minimum data are not provided initially, the report will be considered pending until all attempts to resolve queries for missing data and requests for follow-up information are complete. If, after all attempts at follow-up are made, the minimum criteria are still not met, the report will be considered invalid due to insufficient information. Invalid reports will not be included in the registry analyses.

Analysis Population

The primary population for analysis will include all prospective evaluable participants exposed to IV zanamivir that are not lost to follow-up (i.e., participants with appropriate outcome information that meet the minimum criteria for evaluation). Because early prenatal testing is so frequent, it may be difficult to achieve adequate numbers of pure prospectively identified pregnant women if all pregnancies with prior prenatal testing are excluded from the analysis. Therefore, the primary analysis will include pregnancies enrolled prior to birth outcome but after prenatal testing as well (see definitions of prospective reports).

Secondary analyses may consider additional exposure populations captured through de-identified data sources. For example, UKOSS has ethical approval to collect a minimum exposure and outcome dataset on women exposed to new influenza treatments (including IV zanamivir) with a waiver of informed consent. This will enable capture of some data on women who may be exposed to IV zanamivir during hospitalisation with complicated influenza, but do not consent to participate in this study with more complete data collection. The potential and approach for combined analyses of patient populations, dependent on availability of common variables, will be fully described in the Statistical Analysis Plan.

Exclusions for Analysis Purposes

Invalid registry reports and pregnancies deemed lost to follow-up will be excluded from the primary analysis. Initial analyses will consider prospective and retrospective reports separately unless there is adequate evidence to support lack of bias associated with the retrospective reports. If the anti-influenza treatment to which the woman was exposed cannot be ascertained, an unknown exposure cohort will be established and analysed separately.

Sequential Pregnancies

The number and outcome of sequential pregnancies (subsequent pregnancies within the same woman) will be noted and presented. Sequential pregnancies will be included in the analytic dataset.

Multiple Gestation Pregnancies

The number, type (e.g., twin, triplet), and outcome of multiple gestation pregnancies will be noted and presented. Multiple gestation pregnancies will be included in the analytic dataset. These will be counted as multiple outcomes when the denominator is infant births.

8.7.1. Essential analysis

This registry is primarily descriptive and designed to detect potential safety signals, rather than test hypotheses. GlaxoSmithKline is specifically interested in reporting the prevalence estimates of maternal deaths, birth outcomes and pregnancy outcomes including preterm birth, LBW, SGA and MCMs among pregnancies exposed to IV zanamivir and descriptively comparing them to external comparators to determine whether there is a signal of substantial increased risk with the IV zanamivir exposed group.

Demographic and baseline characteristics will be summarized with simple descriptive statistics and data listings for the evaluable populations of pregnant women and pregnancy outcomes. Demographic and baseline characteristics will also be summarized for the population that is lost to follow-up and compared with the evaluable populations to assess potential differences. These data will be reviewed for potential confounding factors that could affect the interpretation of comparisons of registry outcome prevalence estimates with those of comparators. Further details will be provided in the statistical analysis plan (SAP).

Prevalence point estimates and 95% confidence intervals will be calculated using the binomial distribution for prevalence estimates of maternal deaths, birth outcomes (live births, SAB, IABs, stillbirths) among pregnant women exposed to IV zanamivir and the pregnancy outcomes of preterm birth, LBW and SGA among their live births as well as MCMs among their live births and foetal deaths. For each prevalence estimate, both 1-sided and 2-sided 95% confidence intervals will be calculated and reported. One-sided confidence intervals are appropriate as we are specifically interested in detecting outcome prevalence estimates greater than their respective reference prevalence, and 2-sided confidence intervals will provide further description of the accuracy of the estimates. Prevalence estimates will be reported overall and according to the trimester of IV zanamivir exposure.

The prevalence of maternal deaths and birth outcomes (live births, SABs, IABs, stillbirths) will be calculated as proportions with the number of IV zanamivir exposed pregnancies as the denominator.

The prevalence of preterm births, SGA and LBW will be calculated as proportions, with the number of live births as the denominator. Because MCMs are often associated with preterm birth and LBW, sensitivity analyses will be performed excluding infants with MCMs from the numerator and denominator when prevalence estimates are determined for these outcomes.

Formulas for the calculation of prevalence of the primary outcomes are presented below:

Preterm birth prevalence = $\frac{\text{Number of preterm live births}}{\text{Number of live births}}$

SGA prevalence = $\frac{\text{Number of SGA live births}}{\text{Number of live births}}$

LBW prevalence = $\frac{\text{Number of LBW live births}}{\text{Number of live births}}$

MCM prevalence = $\frac{\text{Number of live births and foetal losses occurring at } \geq 20 \text{ weeks gestation with MCM}}{\text{Number of live births (all) plus number of foetal losses with MCM}}$

Due to inconsistent ascertainment of malformations in early foetal losses these are not included in analyses. Furthermore, a conservative approach is taken to only include foetal losses ≥20 weeks with MCMs, rather than all foetal losses, in the denominator. This will result in an over-estimation of risk.

Because most structural defects have their origins in the first trimester of pregnancy during the period of organogenesis, analyses of MCMs will be stratified by trimester of exposure, if applicable. The second trimester will start at 14 weeks gestation and the third trimester will start at 28 weeks gestation. The prevalence of combined MCMs reported to the registry will be calculated as a proportion with the number of MCMs in live births and foetal losses as the numerator and the number of all live births plus foetal losses with a MCM as the denominator. Pregnancy losses with reported MCMs occurring at or after 20 weeks' gestation will be included in the numerator of the estimate of risk for MCMs to increase sensitivity. The prevalence of combined MCMs in exposed cases will be compared with that reported to EUROCAT AND MACDP. Only cases meeting the EUROCAT criteria will be included in the primary analysis.

As EUROCAT includes chromosomal malformations and MACDP excludes chromosomal malformations, all malformations types will be collected through the registry and the appropriate comparisons will be made with and without chromosomal malformations. There will also be alignment of denominators around inclusion of foetal losses to ensure appropriate comparisons are being made between external reference groups and the registry. Pregnancies exposed to major teratogens (see Section 8.3.3) will be excluded from analyses.

If it is feasible, descriptive comparisons between the registry and an appropriate internal and/or external comparison group will be examined (see Section 8.2 for a description of potential reference groups).

8.7.2. Exploratory analysis

Analyses will be stratified by trimester of exposure and other subgroups of interest, potentially including number of doses of IV zanamivir received, gestational age at enrolment and maternal age. Additional details on subgroup analyses will be described in the SAP. Comparisons may be made to external or internal cohorts, if appropriate.

Additional analyses may stratify by the variables listed below:

- Maternal characteristics (e.g., country)
- Previous pregnancy outcomes (e.g., MCMs, stillbirth)
- Pregnancy complications (e.g., preterm labour, pre-eclampsia, placental abruption)
- Influenza episode (e.g. length of hospital stay, ICU stay, oxygen requirements)
- Co-morbidities (e.g., diabetes, hypertension)
- Concomitant exposures (e.g., teratogenic medications, tobacco)
- Infant/foetus gender and multiple gestations.

8.7.3. General considerations for data analyses

This registry is primarily descriptive and designed to detect potential safety signals, rather than test hypotheses.

8.8. Quality control and Quality Assurance

Ensuring that the data obtained and delivered to GSK are of high quality will be an ongoing, multi-step process involving programming of edit checks for critical data variables in the EDC system and visual review for completeness, logic, consistency, and accuracy. eCRFs will be carefully designed to ensure data quality and integrity.

Investigators must retain all study records required by GSK and by the applicable regulations in a secure and safe facility. The investigator must consult a GSK representative before disposal of any study records and must notify the sponsor of any change in the location, disposition, or custody of the study files. Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced will be retained for a period of 25 years in accordance with Good Pharmacoepidemiological Practice (GPP) guidelines [International Society for Pharmacoepidemiology, 2015]. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution, either directly or through the CRO, as to when these documents no longer need to be retained.

For observational studies, study records or documents may include the analyses files, syntaxes (usually stored at the site of the database), but also questionnaires.

8.9. Limitations of the research methods

The study relies on a sample of exposures identified through UKOSS/INOSS which may or may not be entirely representative of all women exposed to IV zanamivir during pregnancy. However, for a product used under very specific circumstances, this is likely one of the only and most complete methods of obtaining safety information for hospital-based pregnancy exposures.

Because early prenatal testing is so frequent, it may be difficult to achieve adequate numbers of pure prospectively identified pregnant women if all pregnancies with prior prenatal testing are excluded from the analysis. Therefore, the primary analysis will include pregnancies enrolled prior to outcome but after prenatal testing. However, this practice could potentially bias the results by introducing more cases of MCMs identified prenatally [Honein, 1999]. The analysis will attempt to determine bias introduced by this practice by examining the data with and without these cases.

While the registry analysis will initially be limited primarily to prospective reports, some pregnancy exposures may be reported only following pregnancy outcome (retrospective cases). Each retrospective report will be carefully reviewed and an assessment of bias in terms of systematic differences in the outcomes between prospective and retrospective reports will be made. In general, retrospective reports of exposures to medication following notification of outcome are biased toward reporting of the severe and unusual cases and are not reflective of the general experience with the medication.

Given uncertainty around the circumstances when IV zanamivir will be used, it is difficult to define an appropriate comparator group. However, multiple sources of data will be used to estimate background rates of the events of interest in the general population and the feasibility of concurrently enrolling a group of pregnant women with complicated influenza untreated with IV zanamivir will also be explored.

Women may be exposed to additional anti-influenza medications prior to IV zanamivir exposure, the most common class being neuraminidase inhibitors. There is currently no evidence to suggest that exposure to NAIs is associated with adverse pregnancy outcomes so this is unlikely to modify interpretation of risk estimates for IV zanamivir [Graner, 2017].

Finally, there may be differences between countries in how antenatal care is delivered as well as perinatal outcome risks. Some feasibility landscaping work would be useful to reduce potential operational challenges and to assess the background assumptions underlying the sample size calculations.

8.9.1. Study closure/uninterpretability of results

The prevalence of exposure to IV zanamivir is likely to vary across influenza seasons influenced by factors such as the underlying pathogenicity and resistance profiles of circulating virus strains. Accordingly, an update report will be filed with the EMA each year, providing details of the number of treated patients enrolled and guidance on the likely study end date. This will be used to inform on a more realistic study end date. At present 100-150 IV zanamivir exposures are proposed to be sufficient to detect a 2-4-fold

increase in pregnancy outcomes of interest therefore detecting a signal of substantial increase in risk.

8.10. Other aspects

None.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Ethical approval and subject consent

GSK respects the subjects' rights to privacy and will ensure the confidentiality of their medical information in accordance with applicable laws and regulations. Each patient's identity will be known only to the UKOSS/INOSS sites. The registry will assign patient and infant 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 subject identifiers only for both the pregnant mothers and infants.

Each full-time and temporary employee involved with the registry from OXON, UKOSS and INOSS will be fully trained in the protection of human subjects and data privacy and follow established standard operating procedures (SOPs) that outline specifically how to maintain confidentiality and data protection of all registry participants. These SOPs also establish procedures to follow should privacy be compromised in any way. The research staff must be trained and tested on these privacy SOPs annually.

This study is designed and shall be implemented and reported in accordance with GPP, with applicable local regulations and with the ethical principles laid down in the Declaration of Helsinki. The protocol will be submitted for approval to applicable regulatory authorities and appropriate EC prior to registry implementation.

Eligible adults who wish to participate in the registry will be asked to provide informed consent for the collection of their data from their medical records and from the medical records of their infant after birth. Signed informed consent will be obtained in countries where it is required by local laws and regulations. In certain countries, the registry may qualify for verbal informed consent or waiver of documentation of signed informed consent (obtained by the process described below).

The registry will comply with local laws and regulations to facilitate release of participant and infant medical information to the registry.

9.2. Subject confidentiality

Each participant's identity will be known only to UKOSS/INOSS staff enrolling the individual (i.e., participant's HCP), and relevant HCPs (i.e. IV zanamivir prescriber, obstetrician, paediatrician and general practitioner). The registry will assign participant and infant 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 women and infants.

10. LEGAL BASIS FOR PROCESSING INDIVIDUAL HUMAN DATA

The authors confirm that study data is Individual Human Data (IHD) owned by GSK and that:

- The proposed use of the IHD is **Study Use*** as outlined in the patient consent. **OR**
- The study IHD will be anonymised as described in STD_224418. **OR**
- The study IHD use is **Further Research** (as defined in SOP_52209 i.e. the use is anything other than Study Use*) **AND** the research participants consented to their IHD being processed for Further Research and have NOT submitted an Individual Rights Management (IRM) request that limits the use of their IHD.
- *Study Use means – the use of IHD is as stated in the original study protocol and/or aligned with the informed consent form to answer the study objectives and satisfy regulatory requirements and learn more about the product studies and the disease/condition studied. This includes bringing the product to market or maintaining market access which includes working with government agencies, insurers or health care payers and aiding GSK's understanding of clinical efficacy, safety, or effectiveness of the product.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

If, during the study, an adverse event (serious or non-serious) is identified as explicitly attributed to any GSK product (including products not covered in the specific study objective), this will be reported. The study epidemiologist or PV specialist at OXON must forward the report to GSK central safety department within 24 hours of first becoming aware of the event in accordance with SOP_54834 Management of Adverse Event, Pregnancy Exposure, and Incident Reports from Human Subject Research. The same process will be followed for pregnancy exposures or incidents related to any GSK product. On retrospective examination of patient records as part of the study operationalisation, these will also be collected by OXON for inclusion in the study report.

In addition, on retrospective examination of patient records as part of the study operationalisation, all adverse events (AEs) occurring during IV zanamivir exposure window, defined as from the start of treatment to 5 half-lives following the end of treatment, will be collected for inclusion in the study report. This will be equivalent to the collection of AEs between the time of start of treatment to 24 hours after the end of treatment. Due to the high levels of co-morbidities associated with the patient population of interest, AE collection in the mother is reserved to this specific observation period. In addition, adverse events of specific interest in the mother and infant, defined as study objectives and endpoints, will be collected during the study to meet study objectives.

This plan devised by OXON, in compliance with GSK requirement, will include the following elements to ensure a comprehensive approach to safety event collection and reporting:

- Supplier (OXON) pharmacovigilance training
- Investigator and site staff pharmacovigilance training (provided by OXON)
- Safety-specific roles
- AEs, pregnancy exposures, and incidents collection and reporting processes
- AEs, pregnancy exposure, and incident collection forms
- Frequency of data review
- Reporting process and timelines
- Interim reports
- Reconciliation process
- Study-specific PVP monitoring process
- Provision of final study report

The Strengthening the Reporting of Observational studies in Epidemiology (sPVP) or safety management plan will be developed prior to final protocol approval.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1. Target Audience

The EMA, the Committee on Human Medicinal Products (CHMP) and the Pharmacovigilance Risk Assessment Committee (PRAC) will be the primary audience for this study. It will also be of interest to infectious diseases clinicians, obstetricians, paediatricians, teratology specialists, pregnant women and GSK stakeholders such as IV zanamivir project team members, and Global Safety Board. Additionally, this study will contribute novel data to the published literature.

12.2. Study reporting and publications

Key design elements of this registry will be posted in publicly accessible databases including, but not limited to, the European Union Post Authorisation Safety Study (EU PASS) Register. Furthermore, key results of this registry will be posted in publicly accessible databases within the required time-frame from completion of the data collection where applicable and in compliance with current regulations.

Annual updates and final reports will be generated which will be submitted to the relevant regulatory authorities.

The data may also be considered for reporting at scientific conferences or for publication in scientific journals. Preparation of such manuscripts will be prepared independently by

the SAC and in accordance with the current guidelines for STrengthening the Reporting of OBservational studies in Epidemiology [STROBE, 2009]. GSK will be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication.

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ANNEX 1: LIST OF STAND-ALONE DOCUMENTS

None